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TRANSMITTAL OF APPEAL BRIEF

Docket No.
SY9-060RECN

In re Application of: Marvin L. VESTAL

Application No.	Filing Date	Examiner	Group Art Unit
09/755951-Conf. #4499	January 4, 2001	A. Soderquist	1743

Invention: MASS SPECTROMETER SYSTEM AND METHOD FOR MATRIX-ASSISTED LASER DESORPTION MEASUREMENTS

TO THE COMMISSIONER OF PATENTS:

Transmitted herewith is the Appeal Brief in this application, with respect to the Notice of Appeal filed: June 8, 2004 .

The fee for filing this Appeal Brief is $ 500.00 .

[X] Large Entity [ ] Small Entity

[X] A petition for extension of time is also enclosed.

The fee for the extension of time is $ 2,160.00 .

[ ] A check in the amount of _____ is enclosed.

[X] Charge the amount of the fee to Deposit Account No. 12-0080 .
This sheet is submitted in duplicate.

[ ] Payment by credit card. Form PTO-2038 is attached.

[X] The Director is hereby authorized to charge any additional fees that may be required or credit any overpayment to Deposit Account No. 12-0080 .
This sheet is submitted in duplicate.

Dated: January 10, 2005

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I hereby certify that this correspondence is being deposited with the U.S. Postal Service as Express Mail, Airbill No. EV466143385US, in an envelope addressed to: MS Appeal Brief - Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

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Dated: January 10, 2005 Signature: (Michael J. Bastian, Ph.D.)

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPELANTS: Marvin L. Vestal

APPLCIATION NUMBER: 09/755,951 ART UNIT: 1743

FILING DATE: January 4, 2001 EXAMINER: A. Soderquist

TITLE: Mass Spectrometer System and Method for Matrix-Assisted Laser Desorption Measurements

APPEAL BRIEF

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Alexandria, VA 22313-1450

Sir:

This is an appeal from the final rejection of claims 75-87, 90-94, 95 and 97, mailed from the United States Patent and Trademark Office on April 13, 2004. A Notice of Appeal for this application was received by the United States Patent and Trademark Office on June 8, 2004.

A five-month extension of time, for filing the present Appeal Brief is respectfully requested under 37 C.F.R. §§ 47.37(e) and 1.136(a)(1). A petition for the extension of time and appropriate fee are being submitted concurrently herewith. Appellant believes that the present filing necessitates no other fees. However, if any additional fees are due, the Director is hereby authorized to charge any such to Attorney's Deposit Account No. 12-0080, under Order No. SY9-060RECN, from which the undersigned is authorized to draw.

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Table of Contents

Real Party in Interest.....page 3

Related Appeals and Interferences.....page 3

Status of Claims.....pages 3-4

Status of Amendments.....page 4

Summary of Claimed Subject Matter.....pages 4-9

Grounds of Rejection to be Reviewed on Appeal.....page 9

Appellant's Argument.....pages 10-55

Legal Standards and Evidence of Record.....pages 10-14

The Cited References Fail to Teach
or Fairly Suggest all the Limitations of the Claims.....pages 14-29

The Final Office Action Fails
to Establish a Reasonable Expectation of Success.....pages 29-42

The Final Office Action Fails
to Establish a Motivation to Combine.....pages 43-60

Conclusion.....page 61

Claims Appendix.....pages 52-67

Evidence Appendix.....beginning behind page 68

Exhibit A: evidence of the real party in interest.....8 pages

Exhibit B: copy of the Declaration of Robert S. Brown
Under 37 C.F.R. § 1.132, originally submitted July 24, 2003.....32 pages

Exhibit C: copy of the Second Declaration of Robert S. Brown
Under 37 C.F.R. § 1.132, originally submitted March 8, 2004.....36 pages

Exhibit D: U.S. Patent No. 5,045,694.....7 pages

Related Proceedings Appendix.....none

(1) Real Party in Interest

The real parties in interest in the above-identified application are Applera Corporation ("Applera") as successor in interest to PerSeptive Biosystems, Inc. ("PerSeptive Biosystems") and MDS, Inc. ("MDS"). An Assignment perfecting PerSeptive Biosystems' interest in this application was recorded by the United States Patent and Trademark Office ("PTO") on November 11, 1996, at Reel No. 7731, Frame No. 0863. An Assignment perfecting the interest of Applera and MDS was submitted for recordal to the PTO in October 2004. Copies of both Assignments and the PTO-stamped Recordation Form Cover Sheet for the assignment to PerSeptive are provided herewith in the Evidence Appendix as Exhibit A.

(2) Related Appeals and Interferences

To Appellant's knowledge, there are currently no related appeals, interferences, or judicial proceedings which may be related to, directly affect or be directly affected by or have bearing on the Board's decision in the pending appeal.

(3) Status of Claims

Claims 1-74, 88, 89, 96 and 98 have been canceled without prejudice. The claims pending and on appeal are claims 75-87, 90-94, 95 and 97 of the instant application. The rejections of claims 75-87, 90-94, 95 and 97 are being appealed.

Claims 75-81, 84-87, 90-95 and 97 stand rejected under 35 U.S.C. §103(a) as obvious over U.S. Patent No. 5,288,644 to Beavis et al. ("Beavis") in view of "An Automatic Analytical Laboratory for Mass-Spectrometric Isotopic-Dilution Analysis of Uranium and Plutonium in Fuel Solutions," *Safeguards Tech., Proc. Symp.*, 2, pages 165-176 (1970) by Wilhelmi et al. ("Wilhelmi"); U.S. Patent No. 5,382,793 to Weinberger et al. ("Weinberger"); and "Automated Sample Transport System for Chromatography/ Secondary Ion Mass Spectrometry," *Rev. Sci. Instrum.*, 60, pages 1071-1074 (1989) by Duffin et al. ("Duffin").

Claim 82 stands rejected under 35 U.S.C. §103(a) as obvious over Beavis, in view of Wilhelmi, Weinberger, and Duffin, and further in view of U.S. Patent No. 5,037,611 to Ledford, Jr. ("Ledford").

Claim 83 stands rejected under 35 U.S.C. §103(a) as obvious over Beavis, in view of Wilhelmi, Weinberger, and Duffin, and further in view "A direct insertion sample handling system for mass spectrometers," *Int. J. Mass Spectrom. Ion Phys.*, 3, pages 159-160 (1969) by Bakker et al ("Bakker").

(4) Status of Amendments

No amendment has been requested after the Final Office Action dated April 13, 2004.

(5) Summary of Claimed Subject Matter

In accordance with 37 C.F.R. § 41.37(v), Appellant provides a concise explanation of the subject matter defined in each of the independent claims involved in the appeal. As the present application is a reissue application, references to the specification are made by column and line number. The independent claims involved in the appeal are claims 75, 90, 92, 95 and 97. As defined by appealed independent claims 75, 90, 95 and 97 Appellant's inventions relate to systems for obtaining mass data. As defined by appealed independent claim 92 Appellant's invention relates to a method of obtaining mass data.

As defined by appealed independent claim 75, Appellant's invention relates to a system comprising a mass spectrometer comprising an ion source chamber (*see, e.g.,* col. 9, lines 53-54) connected to a vacuum lock chamber (*see, e.g.,* col. 6, lines 52-64; col. 7, lines 1-15; and col. 9, lines 30-44); a laser source in optical communication with the ion source chamber and adapted to provide a laser pulse to a sample support in the ion source chamber (*see, e.g.,* col. 9, lines 48-50; col. 10, lines 3-12; and Figure 9); and a sample support transfer mechanism (*see, e.g.,* col. 8, lines 53-64; and col. 9, lines 3-18 and 38-45). The ion source chamber must comprise at least a sample receiving stage adapted to support a sample support (*see, e.g.,* col. 3, lines 14-17 and 22-34; and col. 6, line 59 to col. 7, line 10), and a mechanism to move the sample receiving stage in an x direction and in a y direction perpendicular to the x direction, wherein the x direction and the y direction lie substantially in the same plane (*see, e.g.,* col. 4, lines 35-38; and col. 9, lines 53-57). In addition, the vacuum lock chamber must comprise at least a sample support holder

adapted to support more than one sample support (*see, e.g.,* col. 6, lines 24-26; and col. 9, lines 38-45).

Moreover, in Appellant's invention as defined by appealed independent claim 75, the sample support transfer mechanism must be adapted to: (a) disassociate a first sample support from the sample receiving stage, transport the first sample support from the ion source chamber through an output port to the vacuum lock chamber and to associate the first sample support with the sample support holder; and (b) disassociate a second sample support from the sample support holder, transport the second sample support from the vacuum lock chamber through the output port to the ion source chamber and to associate the second sample support with the sample receiving stage (*see, e.g.,* col. 8, lines 53-64; and col. 9, lines 3-18 and 38-45).

As defined by appealed independent claim 90, Appellant's invention relates to a system comprising a mass spectrometer comprising an ion source chamber (*see, e.g.,* col. 7, lines 11-14; col. 8, lines 17-21 and 53-54; and col. 9, lines 53-54) connected to a vacuum lock chamber (*see, e.g.,* col. 6, lines 52-64; col. 7, lines 1-15; and col. 9, lines 30-44) and a sample storage chamber connected to the vacuum lock chamber (*see, e.g.,* col. 7, lines 11-14 and 37-41); a laser source in optical communication with the ion source chamber and adapted to provide a laser pulse to a sample support in the ion source chamber (*see, e.g.,* col. 9, lines 48-50; col. 10, lines 3-12; and Figure 9); and a sample support transfer mechanism (*see, e.g.,* col. 8, lines 53-64; and col. 9, lines 3-18 and 38-45). The ion source chamber must comprise at least a sample receiving stage adapted to support a sample support (*see, e.g.,* col. 3, lines 14-17 and 22-34; and col. 6, line 59 to col. 7, line 10), and a mechanism to move the sample receiving stage (*see, e.g.,* col. 4, lines 35-38; and col. 9, lines 53-57). In addition, the sample storage chamber must comprise at least a sample support holder adapted to support at least one sample support (*see, e.g.,* col. 6, lines 24-26 and 52-64; col. 7, lines 1-15; col. 8, lines 1-5; and col. 9, lines 30-37).

Moreover, in Appellant's invention as defined by appealed independent claim 90, the sample support transfer mechanism must be adapted to: (a) disassociate a first sample support from the sample receiving stage, transport the first sample support from the ion source chamber through an output port to the vacuum lock chamber and to associate the first sample support with the sample support holder; and (b) disassociate a second sample support from the sample support holder, transport the second sample support from the vacuum lock chamber through the output port to the ion source

chamber and to associate the second sample support with the sample receiving stage (*see, e.g.,* col. 8, lines 53-64; and col. 9, lines 3-18 and 38-45).

As defined by appealed independent claim 95, Appellant's invention relates to a system comprising a mass spectrometer comprising an ion source chamber (*see, e.g.,* col. 9, lines 53-54) connected to a vacuum lock chamber (*see, e.g.,* col. 6, lines 52-64; col. 7, lines 1-15; and col. 9, lines 30-44); a laser source in optical communication with the ion source chamber and adapted to provide a laser pulse to a sample support in the ion source chamber (*see, e.g.,* col. 9, lines 48-50; and col. 10, lines 3-12); a sample support transfer mechanism (*see, e.g.,* col. 8, lines 53-64; and col. 9, lines 3-18 and 38-45); and a means for maintaining the vacuum lock chamber and the ion source chamber in fluid communication and under a vacuum controlled environment during disassociation, transportation and association of first and second sample supports by the sample support transfer mechanism (*see, e.g.,* col. 9:, lines 39-48).

In Appellant's invention as defined by appealed independent claim 95, the sample support transfer mechanism must be adapted to: (a) disassociate a first sample support from the sample receiving stage, transport the first sample support from the ion source chamber to the vacuum lock chamber and to associate the first sample support with the sample support holder; and (b) disassociate a second sample support from the sample support holder, transport the second sample support from the vacuum lock chamber to the ion source chamber and to associate the second sample support with the sample receiving stage (*see, e.g.,* col. 8, lines 53-64; and col. 9, lines 3-18 and 38-45).

In addition, in Appellant's invention as defined by appealed independent claim 95, the ion source chamber comprises at least a sample receiving stage adapted to support a sample support (*see, e.g.,* col. 3, lines 14-17 and 22-34; and col. 6, line 59 to col. 7, line 10), and a mechanism to move the sample receiving stage in an x direction and in a y direction perpendicular to the x direction, wherein the x direction and the y direction lie substantially in the same plane (*see, e.g.,* col. 4, lines 35-38; and col. 9, lines 53-57). Further, the vacuum lock chamber must comprise at least a sample support holder adapted to support more than one sample support (*see, e.g.,* col. 6, lines 24-26 and 52-64; col. 7, lines 1-15; col. 8, lines 1-5; and col. 9, lines 30-44).

As defined by appealed independent claim 97, Appellants' invention relates to a system comprising a mass spectrometer comprising an ion source chamber (*see, e.g.,* col. 7, lines 11-14; col. 8, lines 17-21 and 53-54; and col. 9, lines 53-54) connected to a vacuum lock chamber (*see, e.g.,* col. 6, lines 52-64; col. 7, lines 1-15; and col. 9, lines 30-44) and a sample storage chamber connected to the vacuum lock chamber; a laser source in optical communication with the ion source chamber and adapted to provide a laser pulse to a sample support in the ion source chamber (*see, e.g.,* col. 9, lines 48-50; col. 10, lines 3-12; and Figure 9); a sample support transfer mechanism (*see, e.g.,* col. 8, lines 53-64; and col. 9, lines 3-18 and 38-45); and a means for maintaining the vacuum lock chamber and the ion source chamber in fluid communication and under a vacuum controlled environment during disassociation, transportation and association of first and second sample supports by the sample support transfer mechanism (*see, e.g.,* col. 9:, lines 39-48).

In Appellant's invention as defined by appealed independent claim 97, the sample support transfer mechanism must be adapted to: (a) disassociate a first sample support from the sample receiving stage, transport the first sample support from the ion source chamber to the vacuum lock chamber and to associate the first sample support with the sample support holder; and (b) disassociate a second sample support from the sample support holder, transport the second sample support from the vacuum lock chamber to the ion source chamber and to associate the second sample support with the sample receiving stage (*see, e.g.,* col. 8, lines 53-64; and col. 9, lines 3-18 and 38-45).

In addition, in Appellant's invention as defined by appealed independent claim 97, the ion source chamber comprises at least a sample receiving stage adapted to support a sample support (*see, e.g.,* col. 3, lines 14-17 and 22-34; and col. 6, line 59 to col. 7, line 10), and a mechanism to move the sample receiving stage (*see, e.g.,* col. 4, lines 35-38; and col. 9, lines 53-57). Further, the sample storage chamber must comprise at least a sample support holder adapted to support at least one sample support (*see, e.g.,* col. 6, lines 24-26 and 52-64; col. 7, lines 1-15; col. 8, lines 1-5; and col. 9, lines 30-44).

As defined by appealed independent claim 92, Appellant's invention relates to a method of obtaining mass data on one or more samples on a sample support associated with the sample receiving stage in an ion source chamber, while other sample supports (themselves containing

one or more samples) are maintained within a vacuum controlled environment in a vacuum lock chamber. The method comprises specific steps for exchanging the sample support associated with the sample receiving stage in the ion source chamber with a sample support from the vacuum lock chamber and obtaining mass data on one or more samples on this new sample support. Specifically, the method of claim 92 comprises the steps of:

- supporting each of a plurality of samples at a fixed location on one of a plurality of sample supports (*see, e.g.,* col. 4, lines 9-17, and Figure 1);
- providing an ion source chamber having a sample receiving stage adapted to support a sample support (*see, e.g.,* col. 3, lines 14-17 and 22-34; and col. 6, line 59 to col. 7, line 10); and
- providing a vacuum lock chamber (*see, e.g.,* col. 6, lines 52-64; col. 7, lines 1-15; and col. 9, lines 30-44) which is adapted to maintain one or more of the sample supports within a vacuum controlled environment while a sample on another of the sample supports is struck by a laser pulse (*see, e.g.,* col. 9:, lines 39-48) and which comprises a sample support holder adapted to receive the plurality of sample supports (*see, e.g.,* col. 6, lines 24-26; and col. 9, lines 38-45).

In addition, in Appellant's invention as defined by appealed independent claim 92, the claimed method of obtaining mass data also comprises the steps of:

- moving a first sample support associated with the sample receiving stage within the ion source chamber in an x direction and in a y direction perpendicular to the x direction (*see, e.g.,* col. 9, lines 61-64; col. 10, lines 7-12; and Figure 9);
- striking with a laser pulse a desired number of the plurality of samples on the first sample support within the ion source chamber to desorb and ionize sample molecules (*see, e.g.,* col. 9, lines 48-50; col. 10, lines 3-12; and Figure 9);
- disassociating the first sample support from the sample receiving stage; and transporting the first sample support from the ion source chamber to the vacuum lock chamber (*see, e.g.,* col. 8, lines 53-64; and col. 9, lines 3-18 and 38-45);
- associating the first sample support with the sample support holder (*see, e.g.,* col. 8, lines 53-64; and col. 9, lines 3-18 and 38-45);

- disassociating a second sample support from the sample support holder; and transporting the second sample support from the vacuum lock chamber to the ion source chamber (*see, e.g.,* col. 8, lines 53-64; and col. 9, lines 3-18 and 38-45);
- associating the second sample support with the sample receiving stage (*see, e.g.,* col. 8, lines 53-64; and col. 9, lines 3-18 and 38-45);
- moving the second sample support associated with the sample receiving stage within the ion source chamber in an x direction, and in a y direction perpendicular to the x direction (*see, e.g.,* col. 9, lines 61-64; col. 10, lines 7-12; and Figure 9); and
- striking with a laser pulse a desired number of the plurality of samples on the second sample support within the ion source chamber to desorb and ionize sample molecules (*see, e.g.,* col. 9, lines 48-50; col. 10, lines 3-12; and Figure 9).

(6) Grounds of Rejection to be Reviewed on Appeal

1. The first ground of rejection to be reviewed on appeal is whether appealed claims 75-87, 90-91, 95 and 97 are patentable under 35 U.S.C. §103(a) over Beavis, in view of Wilhelmi, Weinberger, Duffin, Ledford, and Bakker.

2. The second ground of rejection to be reviewed on appeal is whether appealed claims 92-94 are patentable under 35 U.S.C. §103(a) over Beavis, in view of Wilhelmi, Weinberger, Duffin, Ledford, and Bakker.

3. The third ground of rejection to be reviewed on appeal is whether appealed claim 93 is patentable under 35 U.S.C. §103(a) over Beavis, in view of Wilhelmi, Weinberger, Duffin, Ledford, and Bakker.

4. The fourth ground of rejection to be reviewed on appeal is whether appealed claims 95 and 97 are patentable under 35 U.S.C. §103(a) over Beavis, in view of Wilhelmi, Weinberger, Duffin, Ledford, and Bakker.

5. Although Appellant believes the above-identified grounds of rejection correspond to all the pending rejections, Appellant also appeals any other bases for rejection of the pending claims which were not explicitly stated in the Final Office Action but which may be regarded as still pending.

(7) Appellant's Argument

This is an appeal from the final rejection of claims 75-87, 90-94, 95 and 97, in the Office Action mailed from the United States Patent and Trademark Office on April 13, 2004 ("the Final Office Action"). A Notice of Appeal for this application was received by the United States Patent and Trademark Office on June 8, 2004.

Appellant respectfully requests that the rejection of claims 75-87, 90-94, 95 and 97 under 35 U.S.C. § 103(a) be reversed because the Final Office Action's combination of Beavis, Wilhelmi, Weinberger, Duffin, Ledford and Bakker (collectively "the cited references") is insufficient to either establish a *prima facie* case of obviousness or maintain a rejection under 35 U.S.C. § 103(a). Specifically, the Final Office Action fails to establish a *prima facie* case of obviousness for at least three reasons: (1) the cited references fail to teach or fairly suggest to one of ordinary skill in the art all the limitations of the claimed inventions; (2) the Final Office Action fails to establish that one of ordinary skill in the art would have had a reasonable expectation of successfully combining the cited references to practice the claimed inventions; (3) the Final Office Action fails to establish that one of ordinary skill in the art would have had the requisite motivation to combine the cited references to produce the claimed inventions as a whole.

The following arguments first address in general the legal standards and evidence of record relevant to the present appeal, and then address in particular each of the issues and grounds of rejection to be reviewed on appeal.

(7.1) Legal Standards and Evidence of Record

Three criteria must be met to establish a *prima facie* case of obviousness. First, there must be some motivation to modify or combine the references to provide the claimed device or process. See Graham v. John Deere Co., 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966); In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991); see also MPEP §§ 2142, 2143 (8th Ed., Revision No. 2, May 2004). Second, there must a reasonable expectation of successfully combining the references to provide the claimed device or process. See id. Finally, the combination must teach or fairly suggest all the claim limitations and the invention as a whole. See id. As in all aspects of a *prima facie* case of obviousness, the requisite showings

must be made with respect to the understandings of one of ordinary skill in the art at the time of the invention. See Graham, 383 U.S. at 17-18, 148 USPQ at 467; Al-Site Corp. v. VSI International, Inc., 174 F.3d 1308, 1324, 50 USPQ2d 1161, 1171 (Fed. Cir. 1999); In re Rouffet, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457 (Fed. Cir. 1998); In re Young, 927 F.2d 588, 591, 18 USPQ2d 1089, 1091 (Fed. Cir. 1991); In re Dow Chem. Co., 837 F2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

One of ordinary skill in the art is one who thinks along the line of conventional wisdom in the art. See The Standard Oil Co. v. American Cyanamid Co., 774 F.2d 448, 454, 227 USPQ 293, 298 (Fed. Cir. 1985). A person of ordinary skill in the art is not one who undertakes to innovate, whether by patient, and often expensive, systematic research or by extraordinary insights. See id. The usual way of determining the ordinary skill in the art is with reference to the subjective reaction of a person who was familiar with and practiced the art at the time the invention was made. See, In re Meng, 1492 F.2d 843, 848-49, 181 USPQ 94, 98 (CCPA 1974); see also In re Oerlich, 579 F.2d 86, 91, 198 USPQ 210, 215 (CCPA 1978). First hand practical knowledge of and familiarity with the art at the time of the invention, by an expert, is probative evidence of the state of the art and ordinary skill in the art at the time of the invention. See, In re Piasecki, 745 F.2d 1468, 1473, 223 USPQ 785, 789 (Fed. Cir. 1984).

Accordingly, Appellant respectfully requests that the pending claims be considered in view of all the evidence of record including the two Declarations[1] of Robert S. Brown Under 37 C.F.R. § 1.132 submitted during the prosecution of the present application. The statements of fact, reasoning, observations and views in the Declarations are based on probative evidence and are cognizant of and commensurate with the scope of the claims as evidenced by at least paragraphs 6-8 and 9-12 in the Declarations.

Specifically, the facts, reasoning, observations and views in the Declarations on the state of art, which includes the amount of experimentation needed to modify and combine the cited references, the capabilities of one of ordinary skill in the art, and what one of ordinary skill in the

[1] In the prosecution of the present application two declarations by Prof. Brown were submitted. The first Declaration of Robert S. Brown Under 37 C.F.R. § 1.132, was originally submitted July 24, 2003 ("the First Declaration," a copy of which is attached as Exhibit B) and the Second Declaration of Robert S. Brown Under 37 C.F.R. § 1.132, was originally submitted March 8, 2004, ("the Second Declaration," a copy of which is attached as Exhibit C), collectively referred to herein as "the Declarations."

art would or would not have had a reasonable expectation of successfully doing at the time of the invention, are based on the knowledge and experience of Prof. Brown. Prof. Brown has over 20 years of experience in the mass spectrometry field, and contemporaneous knowledge of both the mass spectrometry field and those of ordinary skill in this field as it existed at the time of the invention. Appellant submits that such first hand practical knowledge of and familiarity with the art at the time of the invention, by an expert, is probative evidence of the state of the art and thus what one of ordinary skill in the art could have or could not have done using knowledge then in the art. See, In re Piasecki, 745 F.2d at 1473, 223 USPQ at 789.

The nature of the matter sought to be established must be taken into consideration in assessing the probative value of an expert declaration. In re Oerlich, 579 F.2d at 91, 198 USPQ at 215. In this case, the declarations of Prof. Brown are introduced, among other things, on the issue of the level of ordinary skill, which is a determination usually made by the subjective reaction of persons who are familiar with and practiced the art at the time the invention was made. See, In re Meng, 1492 F.2d at, 848-49,181 USPQ at 98; see also In re Oerlich, 579 F.2d at 91, 198 USPQ at 215. As such, the statements of fact, reasoning, observations and views of Prof. Brown in the Declarations have a high probative value and are based on his years of experience in the field and contemporaneous direct experience with the field and it practitioners at the time of the invention.

The evidence of Prof. Brown's contemporaneous direct experience with both the field of the claimed invention and its practitioners is extensive and uncontested. The present application claims an effective filing of date of July 21, 1994. In the years 1993-1995 alone, Prof. Brown attended at least ten professional meetings directed to the field of mass spectrometry, was an invited speaker at four professional meetings in the field on topics in mass spectrometry directly related to the present application, coauthored at least four publications with at least three different co-authors, and reviewed a book on "Time-of-Flight Mass Spectrometry and its Applications" published in 1994. See, e.g., the Second Declaration[2] pages 21, 27, 32, and 34. Accordingly, Prof. Brown is familiar with and has first hand knowledge of the state of the art of the field of mass spectrometry at the time of the invention.

[2] Page numbers have been added to the *curriculum vitae* of Prof. Brown attached to the Second Declaration to facilitate reference to the record. The *curriculum vitae* of Prof. Brown starts at page 18 and ends at page 36.

In addition to collaborations with those in the field of mass spectrometry and regular attendance at professional meetings in the field, Prof. Brown has supervised and served as a thesis advisor to graduate students in doctoral programs at Utah State University and Colorado State University since at least 1987. See, e.g., the Declarations at para. 3. In the years 1993-1995, Prof. Brown taught at least eight undergraduate and graduate courses, in which part of the subject matter concerned mass spectrometry. See, the Second Declaration at page 19. Accordingly, Prof. Brown is familiar with and has first hand knowledge of the full spectrum of skill levels of workers in the field of mass spectrometry at the time of the invention including that of the one of ordinary skill in the art. See, e.g., the Declarations at paragraph 3; and the Second Declaration pages 19, 21, 27, 32, and 34.

Prof. Brown has also developed a number of time-of-flight mass spectrometers and mass spectrometry techniques and several laser desorption/ionization time-of-flight mass spectrometers and techniques for their use. See, e.g., the Declarations at para. 2. Accordingly, Prof. Brown is personally familiar with the degree of innovation, effort and experimentation involved in actually conceiving and reducing to practice mass spectrometry instrumentation and techniques for their use.

Based on his over 20 years of experience in the mass spectrometry field, and contemporaneous knowledge of both the mass spectrometry field and practitioners of all skill levels at the time of the invention, Prof. Brown has provided a description of the level of ordinary skill in the pertinent art at the time of the invention. Specifically, Prof. Brown states in the Second Declaration at paragraph 13 that,

> one of ordinary skill in the field of mass spectrometry as it existed on July 21, 1994 would have possessed an education in Chemistry or Physics at a Masters degree level and been competent in the use of mass spectrometry instrumentation. I understand that one of ordinary skill in the art is a "hypothetical person" who does not necessarily exist.

The Final Office Action nowhere provides an alternative description or contests Prof. Brown's description of one of ordinary skill in the art.

The reasoning, observations and views of Prof. Brown in the Declarations are all supported by facts and evidence to the extent possible given the nature of the matter sought to be established, as shall be shown in further detail below. Where the matter is the assertion of the

absence of a teaching or ability, it is illogical to require proof of this negative by reference to texts or descriptions which, by the very nature of the matter sought to be proven, do not exist. Appellant therefore submits that the Declarations constitute probative evidence of at least: (a) the state of the art at the time of the invention; (b) the ordinary level of skill in the art at the time of the invention; (c) the reading one of ordinary skill in the art would give the cited references at the time of the invention; (d) the capabilities of one of ordinary skill in the art at the time of the invention; and (e) what one of ordinary skill in the art would or would not have had a reasonable expectation of successfully doing at the time of the invention. Accordingly, Appellant respectfully requests that the Declarations be given weight in determining each of the issues and grounds of rejection to be reviewed on appeal.

(7.2) The Cited References Fail to Teach or Fairly Suggest all the Limitations of the Claims

Appellant respectfully requests that the rejection of claims 75-87, 90-94, 95 and 97 under 35 U.S.C. § 103(a) be reversed because the cited references, either alone or in proper combination, fail to teach or fairly suggest to one of ordinary skill in the art all the limitations of the claimed inventions. It is well settled that a showing that the prior art provides every limitation of a claim and the invention as a whole is required to establish a *prima facie* case of obviousness. See Graham, 383 U.S. at 17-18, 148 USPQ at 467; Gillette Co. v. S.C.Johnson & Son, Inc., 919 F.2d 720, 724, 16 USPQ2d 1923, 1927 (Fed. Cir. 1990); see also, MPEP §§ 2142, 2143 (8th Ed., Revision No. 2, May 2004). Consequently, the references asserted by the Final Office Action are insufficient to establish a *prima facie* case of obviousness and can not render Appellant's claims obvious.

A determination of whether a reference teaches or suggests to one of ordinary skill in the art an element of a claim and that claim as a whole necessarily requires, among other things, an evaluation of the state of art, the capabilities of one of ordinary skill in the art, and the reading one of ordinary skill in the art would have given the references at the time of the invention. See Graham., 383 U.S. at 17-18, 148 USPQ at 467; Al-Site, 174 F.3d at 1324, 50 USPQ2d at 1171; In re Young, 927 F.2d at 591, 18 USPQ2d at 1091; In re Dow Chem. Co., 837 F.2d at 473, 5 USPQ2d at 1531. The usual way of determining the ordinary skill in the art is with reference to the subjective reaction of a person who was familiar with and practiced the art at the time the

invention was made. See, In re Meng, 1492 F.2d at, 848-49,181 USPQ at 98; see also In re Oerlich, 579 F.2d 86, 91, 198 USPQ 210, 215 (CCPA 1978). First hand practical knowledge of and familiarity with the art at the time of the invention, by an expert, is probative evidence of the state of the art and ordinary skill in the art at the time of the invention. See, In re Piasecki, 745 F.2d at 1473, 223 USPQ at 789.

Prof. Brown has first hand practical knowledge of and familiarity with both the art and its practitioners of ordinary skill at the time of the invention. (see, e.g., the Declarations at paragraphs 2 and 3). Prof. Brown has evaluated the cited references and explicitly described the one of ordinary skill in the art on which his evaluations are based. (see, e.g., the Declarations paragraphs 6 and 7; and the Second Declaration at paragraph 13). The Final Office Action nowhere challenges Prof. Brown's description of one of ordinary skill in the art or provides an alternative description. Accordingly, the observations and views of Prof. Brown are probative evidence on the issue of what the description and terminology in a reference (in view of the state of the art at the time of the invention) would or could convey to those of ordinary skill in the art. See, In re Piasecki, 745 F.2d at 1473, 223 USPQ at 789. It is Prof. Brown's view, with which Appellant agrees, that the cited references fail to teach or suggest to one of ordinary skill in the art all elements as set forth in Appellant's claims 75-87, 90-94, 95 and 97.

(7.2.1) Claims 75-87, 90-91, 95 and 97 are patentable under 35 U.S.C. § 103(a)

Appellant respectfully requests reversal of the final rejections, under 35 U.S.C. § 103(a), of claims 75-87, 90-91, 95 and 97, because the cited references fail to teach or suggest to one of ordinary skill in the art a "sample support transfer mechanism" as set forth in these claims.

Specifically, neither the cited references themselves nor the knowledge generally available in the art suggest a system for obtaining mass data comprising, among other things,

> a sample support transfer mechanism adapted to:
>
> (a) disassociate a first sample support from the sample receiving stage, transport the first sample support from the ion source chamber ...to the vacuum lock chamber and to associate the first sample support with the sample support holder; and
>
> (b) disassociate a second sample support from the sample

> support holder, transport the second sample support from the vacuum lock chamber ... to the ion source chamber and to associate the second sample support with the sample receiving stage

as set forth in independent claims 75, 90, 95 and 97.

(7.2.1.1) ***Beavis Does Not Teach the Sample Support Transfer Mechanism***

Appellant submits that Beavis does not teach or suggest a sample support transfer mechanism as set forth in claims 75-87, 90-91, 95 and 97, and does not believe the Final Office Action asserts otherwise. In particular, the Final Office states at page 9 that,

> Beavis does not provide specific teachings about the mechanism for inserting the sample disk through the vacuum lock into the ion source of the mass spectrometer.

and states at page 10 that,

> Since Beavis fails to teach specifically how to get the disk inside of the mass spectrometer, that would be left up to one of ordinary skill in the art.

Accordingly, Appellant agrees that Beavis fails to teach a sample support transfer mechanism as set forth in claims 75-87, 90-91, 95 and 97.

Further, Appellant submits that Beavis fails to teach or suggest a sample support transfer mechanism as set forth in claims 75-87, 90-91, 95 and 97, because Beavis provides no description or suggestion of the use of a sample support holder in either a vacuum lock chamber connected with the ion source chamber or a sample storage chamber connected to the vacuum lock chamber. As a result, Beavis provides no description or suggestion of the limitations of Appellant's sample transport mechanism which is required to be adapted to, among other things,

> to associate [a] first sample support with [a] sample support holder; and...disassociate a second sample support from the sample support holder,

In support of Appellant's position, Appellant also submits the Declarations, and in the particular at least the facts, reasoning and observations of paragraphs 17-19 of the First Declaration and those of paragraphs 17-20 of the Second Declaration, as evidence that Beavis does not describe a sample transport mechanism as set forth in Appellant's claims 75-87, 90-91,

95 and 97. Appellant respectfully submits that the statements of fact, reasoning, observations, and views of Prof. Brown in the Declarations should be accorded weight on the issue of what Beavis describes and conveys to one of ordinary skill in the art. The nature of the matter sought to be established, i.e., the absence of a teaching in Beavis regarding a sample support transfer mechanism as set forth in Appellant's claims, is necessarily based on the observations and views of Prof. Brown as one with particular contemporaneous knowledge of the art and those of ordinary skill in it because such a matter is the proof of a negative.

Therefore, Appellant submits that Beavis does not teach, suggest or motivate any mechanism or means for moving a sample support to an ion source chamber from another chamber and associating the sample support with a sample receiving stage within the ion source chamber as set forth in Appellant's claims 75-87, 90-91, 95 and 97. Appellant further submits that Weinberger, Wilhelmi, Duffin, Ledford, and Bakker, either alone or in combination, do not cure the deficiencies of Beavis.

(7.2.1.2) Weinberger Does Not Teach the Sample Support Transfer Mechanism

Weinberger does not teach a transport mechanism that can disassociate, transport and associate sample supports as set forth in Appellant's claims 75-87, 90-91, 95 and 97. Weinberger describes a system where a shaft (154) is used to pick up a probe tip (30) from a sample ring (152), the probe tip is then pushed into an ion optics region (32) but the probe remains attached to the shaft during mass spectrometric analysis because it is used to rotate the probe tip which contains the sample for analysis. The shaft (154) has o-ring seals (shown in Figure 6), one of which vacuum isolates the ion optics region (32) from the sample chamber (28) containing the sample ring (152) once the ball valve lock (172) is opened and a probe tip has been fully inserted. This o-ring seal prevents fluid communication between the sample chamber (28) and ion optics region (32) by apparently sealing against the ion optic entrance channel (170) when the ball valve lock (172) is opened and the probe tip is fully inserted. The Weinberger patent's structure of a shaft in a channel prevents x-y translation of the probe during mass spectrometric analysis.

Weinberger illustrates disassociating a sample probe (30) from a sample ring (152) with a push-rod type structure (159, 154), however, despite the Final Office Action's assertion to the

contrary, Weinberger's sample probe is never associated with a sample receiving stage in an ion source chamber because Weinberger's sample probe never leaves the tip of the push-rod until it returns to the sample ring. Specifically, Weinberger at col. 9, lines 23-27, states when referring to Figure 7 that,

> Probe tip **30** may be rotated, as indicated by arrow C [in Figure 7], such that different spaced apart areas **37** of the sample layer, displaced from center **39**, tip face **31** may be irradiated, sequentially, by an irradiating pulse **42**.

Reference to Figure 7 and the accompanying text at col. 8, line 66, to col. 9, line 2, shows that the probe tip **30** of Weinberger is rotated by rotation of the attached push-rod type structure **154**. As a result, the probe tip remains associated with the push rod and is not associated with a sample receiving stage in an ion source chamber. See, also, Weinberger, Fig. 7 and col. 9, lines 5-27 (*indicating* that probe remains attached to tip of push-rod entire time probe undergoes irradiation). Accordingly, Appellant submits that Weinberger does not teach, suggest or motivate a sample support transport mechanism that is adapted to either "disassociate a ... sample support from [a] sample receiving stage," or "associate ... [a] sample support with [a] sample receiving stage" in an ion source chamber as set forth in claims 75-87, 90-91, 95 and 97.

In support of Appellant's position, Appellant also submits the Declarations, and in the particular the facts, reasoning and observations of at least of paragraphs 22-23 of the First Declaration and paragraphs 23-24 of the Second Declaration, as evidence that Weinberger does not describe or suggest a transport mechanism that can disassociate, transport and associate sample supports as set forth in Appellant's claims. Specifically, the First Declaration makes clear in paragraph 23 that, "the Weinberger patent does not describe or suggest a structure that enables a sample support to be dissociated from a transport mechanism and associated with a receiving stage" and the Second Declaration makes clear at paragraph 24 that,

> the Weinberger patent does not describe or suggest a structure that enables a sample support to be dissociated from a transport mechanism and associated with a receiving stage ...the structures described and suggested by the Weinberger patent are incompatible with the use of a receiving stage that provides x-y translation because they technically cannot be made to work with such a receiving stage because modification of the shaft of the Weinberger patent for combination with Beavis to execute x-y translation, would render the mechanism of the Weinberger patent inoperable for its intended purpose.

Appellant respectfully submits that the Declarations should be accorded weight on the issue of what Weinberger describes and conveys to one of ordinary skill in the art. The nature of the matter sought to be established, i.e., the absence of any teaching in Weinberger regarding a sample support transfer mechanism as set forth in Appellant's claims, is necessarily based on the observations and views of Prof. Brown as one with particular contemporaneous knowledge of the art and those of ordinary skill in it because such a matter is the proof of a negative. Nevertheless, to the extent possible, Prof. Brown has made specific reference to the teachings of Weinberger that demonstrate that Weinberger does not teach or suggest a sample transport mechanism adapted to, for example, "associate ... [a] sample support with [a] sample receiving stage" in an ion source chamber as set forth in claims 75-87, 90-91, 95 and 97.

To the extent the Final Office Action's reads Weinberger as describing or suggesting associating a second sample support holder with a sample receiving stage in an ion source chamber when it states, e.g., at page 12, "that samples are associated with (coupled to) and disassociated (separated) from the transfer rod in the process of moving them from their storage location to the ion source," such a reading of Weinberger is unsupported by any facts or description in Weinberger. Weinberger consistently illustrates the probe tip as connected to the push rod during sample irradiation. In addition, to the extent Weinberger discusses the relation of the probe tip to the push rod during sample irradiation, such discussions are inconsistent and contradict any position that asserts the probe tip leaves the push rod or that the probe tip is associated with a sample receiving stage in the ion source chamber of Weinberger.

Therefore, Appellant submits that Weinberger, alone or in combination with Beavis, does not teach or suggest a mechanism or means for moving a sample support to an ion source chamber from another chamber and associating the sample support with a sample receiving stage within the ion source chamber as set forth in Appellant's claims 75-87, 90-91, 95 and 97.

(7.2.1.3) Wilhelmi Does Not Teach the Sample Support Transfer Mechanism

Wilhelmi does not teach or suggest a sample support transport mechanism that is adapted to either "disassociate a ... sample support from [a] sample receiving stage," or "associate ... [a] sample support with [a] sample receiving stage" in an ion source chamber as set forth in claims 75-87, 90-91, 95 and 97. Wilhelmi is concerned with mass spectrometric measurements of

uranium and plutonium in nuclear fuel samples placed as solutions onto evaporator filaments (sample filaments) and dried prior to mass spectrometry analysis. Figure 3 and the accompanying text illustrate a system that uses several mechanisms to move a cassette containing beads of nuclear material where each bead is deposited on heating filament. The Wilhelmi system appears to use a mechanism to place the cassette into a preheating chamber and a mechanism is presumably used to move the heated cassette to a lock chamber. A separate pushrod mechanism is used to push a sample filament (referred to as a "bead" in the article) into the ion source where it is vaporized by heating the filament, which appears to also be referred to as an evaporation filament. The vapor that results is then ionized by electrons emitted by the ionization filament in the ion source (electron impact ionization).

Appellant submits that although Wilhelmi states "[f]rom the lock chamber the individual beads are transported separately by a pinch rod into the ion source for measurement and back to the cassette after measurement," Wilhelmi does not teach or suggest a sample support transfer mechanism adapted to associate a sample support with a sample receiving stage in an ion source chamber. See, Wilhelmi, page 171, section 4.1. Rather, Figure 3 and the context of Wilhelmi read as a whole strongly suggests that the sample support remains attached to the push rod. See also, the First Declaration at para. 20, 21; the Second Declaration at para. 21, 22.

Specifically, Wilhelmi does not teach or suggest that the sample filament ever leaves the push rod for a least three reasons. First, the Wilhelmi article does not mention any separate stage to receive a sample filament. Second, the Wilhelmi article states at page 172 that "as soon as the bead is introduced into the ion source the measurement starts" indicating that the push rod does not detach from the bead (sample filament) during measurement. Third, because there is only one sample filament, sample bead, introduced at a time into the ion source and the sample is vaporized by heating a sample filament, there appears to be no reason to associate the sample filament with a separate stage.

In support of Appellant's position, Appellant also submits the Declarations, and in the particular the facts, reasoning and observations of paragraphs 20-21 in the First Declaration and paragraphs 21-22 in the Second Declaration, as evidence that Wilhelmi does not describe or suggest a transport mechanism that can disassociate, transport and associate sample supports as set forth in Appellant's claims. Specifically, the First Declaration makes clear in paragraph 21,

and the Second Declaration makes clear in paragraph 22, that, "the Wilhelmi article does not describe or suggest that the sample filament (or bead) is ever detached from the end of the pushrod...during mass spectrometric analysis" and provides supporting evidence for this conclusion,

> First, the Wilhelmi article does not mention any separate stage to receive a sample filament. Second, the Wilhelmi article states at page 172 that "as soon as the bead is introduced into the ion source the measurement starts" indicating in my view that the pushrod does not detach from the bead (sample filament) during this step. Third, because there is only one sample filament, sample bead, introduced at a time into the ion source and the sample is vaporized by heating a sample filament, there appears to be no reason to associate the sample filament with a separate stage.

Appellant respectfully submits that the Declarations should be accorded weight on the issue of what Wilhelmi describes and conveys to one of ordinary skill in the art. The nature of the matter sought to be established, i.e., the absence of any teaching in Wilhelmi regarding a sample support transfer mechanism as set forth in Appellant's claims, is necessarily based on the observations and views of Prof. Brown as one with particular contemporaneous knowledge of the art and those of ordinary skill in it because such a matter is the proof of a negative. Nevertheless, to the extent possible, Prof. Brown has made specific reference to the teachings of Wilhelmi that demonstrate that Wilhelmi does not teach or suggest a sample transport mechanism adapted to, for example, "associate ... [a] sample support with [a] sample receiving stage" in an ion source chamber as set forth in claims 75-87, 90-91, 95 and 97.

To the extent the Final Office Action's reads Wilhemli as describing or suggesting associating a second sample support holder with a sample receiving stage in an ion source chamber when it states, e.g., at page 12, "that samples are associated with (coupled to) and disassociated (separated) from the transfer rod in the process of moving them from their storage location to the ion source," such a reading of Wilhelmi is unsupported by any facts or description in Wilhelmi. Wilhelmi illustrates the sample filament as connected to the pinch rod during sample heating and ion formation in the source area. See, e.g., Wilhelmi Figure 3. The fact that Wilhelmi does not explicitly state that the sample filament remains attached to the pinch rod in the ion source, is not a "fact" sufficient to support an assertion by the Final Office Action that

Wilhemli shows the sample filament is associated with a sample receiving stage in the ion source area of Wilhelmi. A substantive positive element of an obviousness case cannot be established by simply reasoning that because a reference does not explicitly preclude a specific meaning it must be suggested that the element be made. See Al-Site, 174 F.3d at 1324, 50 USPQ2d at 1171; In re Rouffet, 149 F.3d at 1357, 47 USPQ2d at 1457-58; In re Vaeck, 947 F.2d at 493, 20 USPQ2d at 1442. Rather, there must be a clear and particular showing that the prior art would have suggested to one of ordinary skill in the art that they should make the claimed device or process as a whole, a showing that the art does not teach away from the claimed invention is insufficient. See id.

Rather, to the extent Wilhelmi provides any implicit information on the relation of the sample filament to the pinch rod during sample heating and ion formation in the source area, such information (see, e.g., Wilhemli page 172, discussed above) suggests that the sample filament remains attached to the pinch rod.

Therefore, Appellant submits that Wilhelmi, alone or in combination with Weinberger and Beavis, does not teach or suggest a mechanism or means for moving a sample support to an ion source chamber from another chamber and associating the sample support with a sample receiving stage within the ion source chamber as set forth in Appellant's claims 75-87, 90-91, 95 and 97.

(7.2.1.4) Duffin, Ledford, and Bakker Do Not Teach the Sample Support Transfer Mechanism

Appellant submits that Duffin does not disclose or suggest any form of sample support transport mechanism and does not believe the Final Office Action asserts otherwise. Appellant submits that Duffin describes a sample translator. (See, e.g., Duffin, Fig. 1 and pages 1072-73; See also, the First Declaration at para. 24; the Second Declaration at para. 25). In addition, Appellant submits the Declarations, and in the particular the facts, reasoning and observations of paragraph 24 in the First Declaration and of paragraph 25 in the Second Declaration, as evidence that Duffin does not describe or suggest a transport mechanism that can disassociate, transport and associate sample supports as set forth in Appellant's claims. Moreover, even if Duffin's sample translator is considered to teach a sample receiving stage, Duffin provides no teaching,

suggestion or motivation of any mechanism adapted to disassociate or associate a sample support with a sample receiving stage, or to transport the sample support to a sample receiving stage. Accordingly, Duffin does not teach, suggest or motivate the sample support transport mechanism required by Appellant's claims 75-87, 90-91, 95 and 97.

Appellant submits that Ledford does not disclose or suggest any form of sample support transport mechanism and does not believe the Final Office Action asserts otherwise. Rather, the Final Office Action appears to assert Ledford only against claim 82 with respect to the use of indicia to provide indexing and sample information. In support of Appellant's position, Appellant submits the Declarations, and in the particular the facts, reasoning and observations of paragraph 25 in the First Declaration and of paragraph 26 in the Second Declaration, as evidence that Ledford does not describe or suggest a transport mechanism that can disassociate, transport and associate sample supports as set forth in Appellant's claims.

Appellant submits that Bakker does not disclose or suggest any form of sample support transport mechanism and does not believe the Final Office Action asserts otherwise. Rather, the Final Office Action appears to assert Bakker only against claim 83 to illustrate a system with a swing butterfly valve. Appellant admits that while swing butterfly valves and other vacuum isolation methods such as gate valves and ball valves would have been known to practitioners of ordinary skill in the field of mass spectrometry, the Bakker article also does not provide any suggestion or description that would have provided guidance to the one of ordinary skill in the art on how to make or use a mechanism that could transport sample supports to and from an ion source chamber through an output port to a vacuum lock chamber and to associate and dissociate sample supports with a sample support holder and sample receiving stage as set forth in claims 75-87, 90-91, 95 and 97. In support of Appellant's position, Appellant submits the Declarations, and in the particular the facts, reasoning and observations of paragraph 26 in the First Declaration and of paragraph 27 in the Second Declaration, as evidence that Bakker does not describe or suggest a transport mechanism that can disassociate, transport and associate sample supports as set forth in Appellant's claims.

(7.2.2) Claims 92-94 are patentable under 35 U.S.C. § 103(a)

Appellant respectfully requests reversal of the final rejections, under 35 U.S.C. § 103(a), of claims 92-94 because the cited references fail to teach or suggest to one of ordinary skill in the art at least the steps of disassociating, transporting, and associating first and second sample supports as set forth in these claims. Specifically, the cited references fail to teach, suggest or motivate a method of obtaining mass data that includes at least the steps of:

- disassociating [a] first sample support from [a] sample receiving stage;
- transporting the first sample support from [an] ion source chamber to [a] vacuum lock chamber;
- associating the first sample support with [a] sample support holder;
- disassociating a second sample support from the sample support holder;
- transporting the second sample support from the vacuum lock chamber to the ion source chamber; [and]
- associating the second sample support with the sample receiving stage.

as set forth in claims 92-94 (referred to hereafter for the sake of conciseness as "the sample transfer steps"). For the reasons discussed herein with respect to claims 75-87, 90-91 and 95-97, in the context of a sample transport mechanism, the cited references fail to teach the dissociating, transporting, associating of first and second sample supports as set forth in claims 92-94 because the cited references provide no description or suggestion of a mechanism which could do so or a method which does so. In support of Appellant's position, Appellant submits the Declarations, and in the particular the facts, reasoning and observations of paragraphs 17-29 in the First Declaration, and paragraphs 17-30 in the Second Declaration, as evidence that the cited references do not describe or suggest the steps of disassociating, transporting, and associating first and second sample supports as set forth in claims 92-94.

(7.2.3) Claim 93 is further patentable under 35 U.S.C. § 103(a)

Appellant respectfully requests reversal of the final rejections, under 35 U.S.C. § 103(a), of claim 93, because, in addition to the reasons set forth elsewhere herein, the cited references fail to teach or suggest to one of ordinary skill in the art at least the steps of claim 92 in combination with the condition,

> wherein the vacuum lock chamber and ion source chamber are in fluid communication and are maintained under a vacuum controlled environment during the dissociating, transporting, and associating of the first and second sample supports.

as set forth in claim 93 (referred to hereafter for the sake of conciseness as "the vacuum controlled environment condition").

Specifically, Appellant submits that Beavis does not teach or suggest a sample support transfer mechanism as set forth in claims 75-87, 90-91, 95 and 97, and does not believe the Final Office Action asserts otherwise. In particular, the Final Office states at page 9 that,

> Beavis does not provide specific teachings about the mechanism for inserting the sample disk through the vacuum lock into the ion source of the mass spectrometer.

and states at page 10 that,

> Since Beavis fails to teach specifically how to get the disk inside of the mass spectrometer, that would be left up to one of ordinary skill in the art.

Accordingly, Appellant agrees that Beavis fails to teach a sample support transfer mechanism as set forth in claims 75-87, 90-91, 95 and 97.

As Beavis fails to teach a sample support transfer mechanism, the only mechanism or method remaining for the transporting a sample disk into the ion source, or dissociating or attaching of the sample disk to the stepper motor is manual operator intervention. As is clear to one of ordinary skill in the art, the manual performance of such activities cannot be done in a vacuum controlled environment without exposing the operator to the very harmful effects of vacuum. None of Wilhelmi, Weinberger, Duffin, Ledford or Bakker cure this deficiency. Therefore, Beavis can not be said to teach or suggest the vacuum controlled environment condition as set forth in claim 93.

Further, in support of Appellant's position, Appellant also submits the Declarations, and

in the particular the facts, reasoning and observations of paragraph 28 in the Second Declaration, as evidence that Beavis does not describe or suggest the vacuum controlled environment condition as set forth in claim 93. Specifically, Prof. Brown in the Second Declaration at paragraph 28 observes,

> Based on my experience, there is no equivalent operator hands-on activity to [the sample transfer steps] while the vacuum lock chamber and the ion source chamber are in continuous fluid communication and under a vacuum controlled environment during disassociation, transportation and association of the sample supports without exposing the operator to the detrimental effects of vacuum.

(emphasis added). The text of Beavis further indicates that the vacuum controlled environment condition as set forth in claim 93 is not met because, as Prof. Brown observes in the Declarations at paragraph 17,

> I can find no description in the Beavis patent that describes how one could either attach or detach the sample disk of Beavis to the stepper motor under a vacuum controlled environment. It is my view that Beavis indicates that attachment and detachment do not occur under a vacuum controlled environment at column 4, lines 65-67, when he instructs that, "any gas introduced in this procedure [the insertion of a disk into the ion source] must be removed prior to measuring the mass spectrum," and at column 5, lines 25-29, where Beavis indicates that pumpdown is required after inserting a new sample disk, "less than five minutes of each two hour period is required for loading and pumpdown."

(emphasis added). Accordingly, if pumpdown is required after the process, vacuum was not maintained and as a result the process did not and could not have occurred under a vacuum controlled environment.

To the extent the Final Office Action asserts that Bakker cures the deficiencies of Beavis when asserting at page 11 of the Final Office Action that Bakker,

> clearly shows that the pump down occurs between the time the sample enters the vacuum lock and the time that the ion source chamber is opened to the vacuum lock chamber for the sample being inserted into the ion source chamber. From this is clear that the Beavis reference discussion the pump down cannot be used to show that the attachment and detachment of the sample disk to the stepper motor occur either inside or outside of the ion source

Appellant must respectfully disagree. First, the Final Office Action has provided no showing how the Bakker reference, published 25 years before the issuance of Beavis, can be read to describe Beavis. Second, Appellant submits that this description of Bakker by its own words indicates that "pump down occurs between the time the sample enters the vacuum lock and the time that the ion source chamber is opened;" and accordingly, vacuum was not maintained. As a result, the process of Bakker did not and could not have occurred under a under a vacuum controlled environment.

(7.2.4) ***Claims 95 and 97 are further patentable under 35 U.S.C. § 103(a)***

Appellant respectfully requests reversal of the final rejections, under 35 U.S.C. § 103(a), of claims 95 and 97, because, in addition to the reasons set forth elsewhere herein, the cited references fail to teach or suggest to one of ordinary skill in the art a "sample support transfer mechanism" in combination with a,

> means for maintaining the vacuum lock chamber and the ion source chamber in fluid communication and under a vacuum controlled environment during disassociation, transportation and association of the first and second sample supports

as set forth in claims 95 and 97 (referred to hereafter for the sake of conciseness as "the vacuum controlled environment limitation").

Appellant submits that Beavis does not teach or suggest a sample support transfer mechanism as set forth in claims 75-87, 90-91, 95 and 97, and does not believe the Final Office Action asserts otherwise. Accordingly, Appellant agrees that Beavis fails to teach a sample support transfer mechanism as set forth in claims 75-87, 90-91, 95 and 97.

As Beavis fails to teach a sample support transfer mechanism, the only mechanism remaining for the transporting a sample disk into the ion source, or dissociating or attaching of the sample disk to the stepper motor is manual operator intervention. As is clear to one of ordinary skill in the art, the manual performance of such activities cannot be done in a vacuum controlled environment without exposing the operator to the very harmful effects of vacuum. None of Wilhelmi, Weinberger, Duffin, Ledford or Bakker cure this deficiency. Therefore, Beavis can not be said to teach or suggest the vacuum controlled environment limitation as set forth in claims 95 and 97.

Further, in support of Appellant's position, Appellant also submits the Declarations, and in the particular the facts, reasoning and observations of paragraph 28 in the Second Declaration, as evidence that Beavis does not describe or suggest the vacuum controlled environment limitation as set forth in claims 95 and 97. Specifically, Prof. Brown in the Second Declaration at paragraph 28 observes,

> Based on my experience, there is no equivalent operator hands-on activity to [the sample support transfer mechanism] while the vacuum lock chamber and the ion source chamber are in continuous fluid communication and under a vacuum controlled environment during disassociation, transportation and association of the sample supports without exposing the operator to the detrimental effects of vacuum.

(emphasis added). The text of Beavis further indicates that the vacuum controlled environment limitation as set forth claims 95 and 97 is not met because, as Prof. Brown observes in the Declarations at paragraph 17,

> I can find no description in the Beavis patent that describes how one could either attach or detach the sample disk of Beavis to the stepper motor under a vacuum controlled environment. It is my view that Beavis indicates that attachment and detachment do not occur under a vacuum controlled environment at column 4, lines 65-67, when he instructs that, "any gas introduced in this procedure [the insertion of a disk into the ion source] must be removed prior to measuring the mass spectrum," and at column 5, lines 25-29, where Beavis indicates that pumpdown is required after inserting a new sample disk, "less than five minutes of each two hour period is required for loading and pumpdown."

(emphasis added). Accordingly, if pumpdown is required after the process, vacuum was not maintained and as a result the process did not and could not have occured under vacuum controlled environment.

To the extent the Final Office Action asserts that Bakker cures the deficiencies of Beavis when asserting at page 11 of the Final Office Action that Bakker,

> clearly shows that the pump down occurs between the time the sample enters the vacuum lock and the time that the ion source chamber is opened to the vacuum lock chamber for the sample being inserted into the ion source chamber. From this is clear that the Beavis reference discussion the pump down cannot be used to show that the attachment and detachment of

> the sample disk to the stepper motor occur either inside or outside of the ion source

Appellant must respectfully disagree. First, the Final Office Action has provided no showing how the Bakker reference, published 25 years before the issuance of Beavis, can be read to describe Beavis. Second, Appellant submits that this description of Bakker by its own words indicates that "pump down occurs between the time the sample enters the vacuum lock and the time that the ion source chamber is opened;" and accordingly, vacuum was not maintained. As a result the process of Bakker did not and could not have occured under a under a vacuum controlled environment.

(7.3) The Final Office Action Fails to Establish a Reasonable Expectation of Success

Appellant respectfully submits that to combine two or more of Beavis, Weinberger, Wilhelmi, Duffin, Ledford, and Bakker (collectively "the cited references") to produce one or more of Appellant's claims 75-87, 90-94, 95 and 97 would require undue experimentation by one of ordinary skill in the art.

To establish a *prima facie* case of obviousness, there must be a particular showing why one of ordinary skill in the art would have had a reasonable expectation of producing the claimed invention as a whole and not just an assertion that the prior art could be combined to produce the claimed invention. See In re Dow Chem. Co., 837 F.2d at 473, 5 USPQ2d at 1531; Ex Parte Marinacco, 10 USPQ2d 1716, 1717 (BPAI 1989). The test is not what one of ordinary skill in the art could do; but rather, what one of ordinary skill in the art would have had a reasonable expectation of doing without undue experimentation. See id.

The Final Office Action fails to establish a *prima facie* case of obviousness because it provides no evidence that one of ordinary skill in the art would have had a reasonable expectation of successfully modifying and combining the cited references to produce any one of Appellant's claims as a whole. The Final Office Action appears to assert that because the references fall in the field of the invention and allegedly show all the elements of the invention that one of ordinary skill in the art would necessarily be able to [could] combine them to produce Appellant's claimed inventions as a whole. What one of ordinary skill in the art could do is simply not determinative of, or the test for, whether a reasonable expectation of success exists.

See In re Dow Chem. Co., 837 F.2d at 473, 5 USPQ2d at 1531; Ex Parte Marinacco, 10 USPQ2d at 1717. It is axiomatic that a claimed invention is not obvious solely because all the elements are found in the prior art and because they could be combined (because, e.g., the inventors of the claim have evidently done so). See Life Technologies, Inc. v. Clontech Laboratories, Inc., 224 F.3d 1320, 1326, 56 USPQ2d 1186, 1190 (Fed. Cir. 2000).

A determination of whether a reasonable expectation of success exists necessarily requires, among other things, an evaluation of the state of art (which includes the amount of experimentation needed to modify and combine the cited references), the capabilities of one of ordinary skill in the art, and what one of ordinary skill in the art would or would not have had a reasonable expectation of successfully doing (not what they could have done). See Graham., 383 U.S. at 17-18, 148 USPQ at 467; Life Technologies, 224 F.3d at 1326, 56 USPQ2d at 1190, 1191; Al-Site Corp., 174 F.3d at 1324, 50 USPQ2d at 1171; In re Dow Chem. Co., 837 F.2d at 473, 5 USPQ2d at 1531; Ex Parte Marinacco, 10 USPQ2d at 1717. The usual way of determining the ordinary skill in the art is with reference to the subjective reaction of a person who was familiar with and practiced the art at the time the invention was made. See, In re Meng, 1492 F.2d at, 848-49,181 USPQ at 98; see also In re Oerlich, 579 F.2d at 91, 198 USPQ at 215. First hand practical knowledge of and familiarity with the art at the time of the invention, by an expert, is probative evidence of the state of the art and ordinary skill in the art at the time of the invention. See, In re Piasecki, 745 F.2d at 1473, 223 USPQ at 789.

Prof. Brown has first hand practical knowledge of and familiarity with both the art and its practitioners of ordinary skill at the time of the invention, as well as practical hands-on experience in the development of mass spectrometry instrumentation. See, e.g., the Declarations at paragraphs 2 and 3. Prof. Brown has evaluated the cited references and explicitly described the one of ordinary skill in the art on which his evaluations are based. See, e.g., the Declarations paragraphs 6 and 7; and the Second Declaration at paragraph 13. The Final Office Action nowhere challenges Prof. Brown's description of one of ordinary skill in the art or provides an alternative description. Accordingly, the observations and views of Prof. Brown, as one with particular contemporaneous knowledge of the art and those of ordinary skill in it, are probative evidence on the degree of innovation, effort and experimentation involved in actually conceiving and reducing to practice mass spectrometry instrumentation and techniques for their use. See, In

re Piasecki, 745 F.2d at 1473, 223 USPQ at 789. Thus, the observations and views of Prof. Brown are probative evidence on the issue of reasonable expectation of success. See, id.

Appellant respectfully submits that to combine two or more of the cited references to produce one or more of Appellant's claims 75-87, 90-94, 95 and 97 would require undue experimentation by one of ordinary skill in the art; a position which is supported by the facts, reasoning, observations and views of Prof. Brown. Specifically, Prof. Brown at paragraph 29 in the Second Declaration states:

> ...the likelihood that one of ordinary skill in the field of mass spectrometry as of July 21, 1994, would have been able to modify and combine the cited references to produce one or more of the Vestal systems was remote [and]...would not have had a reasonable expectation of successfully combining the cited references to produce one or more of the Vestal systems...any expectation of success by one of ordinary skill in the field would have been unreasonable because it would have required extensive experimentation to determine how to modify and then modify and combine existing components [because]... the cited references and to my knowledge the mass spectrometry field as of July 21, 1994, provided no[: **(a)**] working examples of a transfer mechanism such as the Vestal transfer mechanism[; or **(b)**] guidance on how such existing components could be modified and combined to produce one or more of the Vestal systems.

(see also, e.g., Second Declaration paragraphs 9 and 15 explaining Prof. Brown's use of the shorthand terms "Vestal transfer mechanism," and "Vestal systems;" see also Second Declaration paragraphs 10, 16, and 30, for specific reference to the method claims). Prof. Brown has clearly articulated examples of why undue experimentation would have been required by one of ordinary skill in the art to produce one or more of Appellant's claims, specifically, the prior art provided no working examples or guidance on how to conduct the modifications necessary to produce one or more of Appellant's claimed inventions. As a result, one of ordinary skill in the art would have needed to innovate (either by extensive experimentation or extraordinary insight) to arrive at the modifications necessary to produce one or more of Appellant's claimed inventions. Accordingly, one of ordinary skill in the art could not have had a reasonable expectation of successfully arriving at one or more of the claimed inventions because one of ordinary skill in the art is not one who undertakes to innovate either by extensive experimentation or extraordinary insight. See Standard Oil, 774 F.2d at 454, 227 USPQ at 298.

The reasoning, observations and views of Prof. Brown are based at least on the same evidence as consider by the Final Office Action. (see, e.g., The Declarations paragraphs 6 and 7). The record contains no affidavit or assertion that the Final Office Action is based on facts outside of the cited references. Specifically, the record contains no affidavit or assertion that the Final Office Action is based on personal knowledge of the Examiner of either the art or its practitioners at the time of the invention. The Final Office Action does not contest the qualifications, knowledge or veracity of Prof. Brown. The Final Office Action does not challenge the description of one of ordinary skill in the art provided by Prof. Brown or provides an alternative description. Accordingly, the Final Office Action does not contest the facts or evidence on which Prof. Brown bases his evaluations, or provide additional facts not considered by Prof. Brown.

In fact, the conclusions of the Final Office Action are based on fewer facts and less evidence than those of Prof. Brown because on the record the Examiner does not asset to have personal knowledge of either the art or its practitioners at the time of the invention. As a result, the Final Office Action has no basis for substituting its judgment for that of Prof. Brown on matters of the state of the art, the ordinary level of skill in the art, the capabilities of one of ordinary skill in the art, and what one of ordinary skill in the art would or would not have had a reasonable expectation of successfully doing at the time of the invention. Accordingly, the conclusions of the Final Office Action are unsustainable in view of the Declarations of Prof. Brown. See, In re Zeidler, 682 F.2d 961, 966, 967, 215 USPQ 490, 494 (CCPA 1982). Nevertheless, the Final Office Action contests the conclusions of Prof. Brown regarding what one of ordinary skill in the art would or would not have had a reasonable expectation of successfully doing.

In rebuttal to Appellant's position and the Declarations of Prof. Brown, the Final Office Action states at page 12 that,

> both the Wilhelmi and Weinberger references teach that the samples are associated with (coupled to) and disassociated (separated) from the transfer rod in the process of moving them from their storage location to the ion source. Thus one of skill in the art certainly knows how to associate and disassociate the sample under a vacuum environment in a mass spectrometer. This coupled with the Beavis reference showing the sample

> disk located inside the ion source chamber shows that one of ordinary skill in the art has the knowledge and ability to provide means to associate and disassociate the sample disk with a sample receiving stage in a vacuum chamber such as the ion source of a mass spectrometer

Appellant agrees that Wilhelmi and Weinberger show samples attached to a pushrod and that Beavis shows a disk attached to a stepper motor. However, these simple schematic illustrations and their descriptions belie the complexity of the actual instruments and do not establish that one of ordinary skill in the art would have been able to bridge the gap between Beavis, Weinberger and Wilhelmi without undue experimentation. The cited references themselves do not convey how difficult it would be to modify them or provide guidance on how to do so.

The Final Office Action appears to assert at page 11 (citing *In re Sovish*, 226 USPQ 771 (Fed. Cir. 1985)) that once one of ordinary skill in art has knowledge of the structures that could allegedly be modified to produce elements of Appellant's claims, that the ordinary artisan would then necessarily reasonably expect to be able to modify and combine them to practice Appellant's claims because one of ordinary skill is viewed as having skill. Appellant's do not disagree that one of ordinary skill is viewed as having ordinary skill. Rather, Appellant must disagree with the Final Office Action's assumption that the ordinary artisan would be able to modify and combine the cited references without undue experimentation to practice Appellant's claims. The only evidence that the Final Office Action has put forward for this assumption are the Beavis, Weinberger and Wilhelmi references themselves, although such modifications are nowhere illustrated or described in the cited references. The Final Office Action simply assumes that modification would be within the skill of one of ordinary skill in the art without any reference to what that level of skill is or the level of skill needed to modify the cited references.

To address the Final Office Actions implicit criticism of Prof. Brown's Declarations; certainly, a determination that a modification required undue experimentation could be made, e.g.,: if one or more ordinary artisans had tried, failed, and reported their failure in the literature; an aptitude test existed for mass spectrometric instrument development; or if the art believed it could not be done. However, probative evidence is not limited to a showing of documentary evidence, statistical evidence or explicit teachings away. See, In re Meng, 1492 F.2d at, 848-49,181 USPQ at 98; see also In re Oerlich, 579 F.2d at 91, 198 USPQ at 215. As has been established by the Courts, first hand practical knowledge of and familiarity with the art at the

time of the invention, by an expert, is probative evidence of the state of the art (which includes the amount of experimentation needed to modify and combine the cited references) and ordinary skill in the art at the time of the invention. See, In re Piasecki, 745 F.2d at 1473, 223 USPQ at 789. Accordingly, Appellant must disagree with the Final Office Action's implication that the observations and views of Prof. Brown do not constitute probative evidence on whether a modification of the prior art would require undue experimentation by one of ordinary skill.

The Declarations of Prof. Brown are probative evidence and are grounded on facts in the record. It is a fact that Prof. Brown's contemporaneous direct experience with both the field of the claimed invention and its practitioners is extensive and uncontested, having regularly published and attended meetings in the field in the years 1993-1995. See, e.g., the Second Declaration pages 21, 27, 32, and 34. It is not a fact of record that the Examiner has contemporaneous direct experience with both the field of the claimed invention and its practitioners. It is a fact that Prof. Brown is familiar with and has first hand knowledge of the skill level of the one of ordinary skill in the art and the capabilities that implies. See, e.g., the Declarations at paragraph 3; and the Second Declaration pages 19, 21, 27, 32, and 34. It is not a fact of record that the Examiner has first hand knowledge of the skill level of the one of ordinary skill in the art and the capabilities that implies. It is a fact that Prof. Brown is personally familiar with the degree of effort and experimentation involved in actually conceiving and reducing to practice mass spectrometry instrumentation and techniques for their use, having developed a number of time-of-flight mass spectrometers and mass spectrometry techniques and several laser desorption/ionization time-of-flight mass spectrometers and techniques for their use. See, e.g., the Declarations at paragraph 2. It is not a fact of record that the Examiner is personally familiar with the degree of effort and experimentation involved in actually conceiving and reducing to practice mass spectrometry instrumentation and techniques for their use. It is a fact that Prof. Brown had not seen, at the time of the invention any mass spectrometric instrument that practiced Appellant's claims, as evidence by Prof. Brown's sworn statement that,

> the steps necessary to modify such existing components and produce an instrument in keeping with one or more of the Vestal systems, were not known, and would not have been apparent to one of ordinary skill in the mass spectrometry field as of July 21, 1994, without the disclosure provided by the Vestal application

(the First Declaration at paragraph 27, the Second Declaration at paragraph 29).

Further, the Declarations of Prof. Brown are probative evidence and grounded on relevant facts in the record because Prof. Brown has clearly articulated what the level of ordinary skill in the art is; (see, e.g., the Second Declaration at paragraph 13); evaluated the teachings of the references in light of the knowledge available to one of ordinary skill in the art at the time of the invention (see, e.g., the Declarations at paragraphs 6-8 and 15 et seq.) and compared this to the claimed inventions (see, e.g., the Declarations at paragraphs 9-12 and 26 et seq.) based on his first hand contemporaneous knowledge. To the extent that all declarations express opinions, the statements of Prof. Brown are of one conceded to be extensively familiar with both the art and its practitioners at the time of the invention. Accordingly, Appellant must disagree with the Final Office Action's assertion that the observations and views of Prof. Brown do not constitute probative evidence on whether a modification of the prior art would require undue experimentation by one of ordinary skill. See, In re Piasecki, 745 F.2d at 1473, 223 USPQ at 789.

Appellants respectfully submit that the burden is on the examiner to "support the conclusion that the claimed invention is directed to obvious subject matter" Ex parte Clapp, 227 USPQ at 973; MPEP § 706.02 (j) (8th Ed., Revision No. 2, May 2004). This the Final Office Action has not done in view of the reasons set forth herein and the Declarations of Prof. Brown. Therefore, Appellant respectfully submits that the Final Office Action fails to establish a *prima facie* case that one of ordinary skill in the art would have had a reasonable expectation of successfully producing any of the inventions in Appellant's claims 75-87, 90-94, 95 and 97 as a whole. See Graham., 383 U.S. at 17-18, 148 USPQ at 467; Al-Site, 174 F.3d at 1324, 50 USPQ2d at 1171; In re Dow Chem. Co., 837 F.2d at 473, 5 USPQ2d at 1531; In re Zeidler, 682 F.2d at 966, 967, 215 USPQ at 494; Ex parte Marinacco, 10 USPQ2d at 1717.

(7.3.1) Claims 75-87, 90-91, 95 and 97 are patentable under 35 U.S.C. § 103(a)

Appellant respectfully requests reversal of the final rejections, under 35 U.S.C. § 103(a), of claims 75-87, 90-91, 95 and 97, because one of ordinary skill in the art would not have had a reasonable expectation of practicing a "sample support transfer mechanism" as set forth in these

claims as a whole. In support of Appellant's position, Appellant submits the Declarations, and in the particular the facts, reasoning and observations of paragraphs 17-28 in the First Declaration, and paragraphs 17-29 in the Second Declaration, as evidence that one of ordinary skill in the art would not have had a reasonable expectation of successfully modifying and combining two or more of the cited references to produce one or more of claims 75-87, 90-91, 95 and 97 and that such modification and combination would require undue experimentation by one of ordinary skill in the art.

Specifically, neither the cited references themselves nor the knowledge generally available in the art would have enabled one of ordinary skill in the art to produce without undue experimentation a system for obtaining mass data comprising, among other things,

> a sample support transfer mechanism adapted to:
>
> (a) disassociate a first sample support from the sample receiving stage, transport the first sample support from the ion source chamber ...to the vacuum lock chamber and to associate the first sample support with the sample support holder; and
>
> (b) disassociate a second sample support from the sample support holder, transport the second sample support from the vacuum lock chamber ... to the ion source chamber and to associate the second sample support with the sample receiving stage

as set forth in independent claims 75, 90, 95 and 97. As set forth elsewhere herein, Beavis, alone or in combination with the knowledge of the art and one or more of Weinberger, Wilhelmi, Duffin, Ledford, and Bakker, do not teach or suggest a "sample support transfer mechanism," as set forth in Appellant's claims 75-87, 90-91, 95 and 97.

Appellant submits that Beavis does not teach, suggest, or provide guidance on making a sample support transfer mechanism as set forth in claims 75-87, 90-91, 95 and 97, and does not believe the Final Office Action asserts otherwise. In particular, the Final Office states at page 9 that,

> Beavis does not provide specific teachings about the mechanism for inserting the sample disk through the vacuum lock into the ion source of the mass spectrometer.

and states at page 10 that,

> Since Beavis fails to teach specifically how to get the disk inside of the mass spectrometer, that would be left up to one of ordinary skill in the art.

Accordingly, Appellant agrees that Beavis fails to provide one of ordinary skill in the art with a reasonable expectation of successfully producing a sample support transfer mechanism as set forth in claims 75-87, 90-91, 95 and 97.

Appellant submits that Weinberger fails to provide one of ordinary skill in the art with a reasonable expectation of successfully producing a sample support transfer mechanism as set forth in claims 75-87, 90-91, 95 and 97. Appellant submits that the illustration and description of a sample which remains attached to a pushrod in the ion optics region is not sufficient to provide one of ordinary skill in the art with a reasonable expectation that they could have modified Weinberger to provide a sample support transfer mechanism as set forth in claims 75-87, 90-91, 95 and 97. In support of Appellant's position, Appellant also submits the Declarations, and in the particular the facts, reasoning and observations of at least of paragraphs 22-23 of the First Declaration and paragraphs 23-24 of the Second Declaration, as evidence that Weinberger does not describe or suggest a transport mechanism that can disassociate, transport and associate sample supports as set forth in Appellant's claims. Specifically, the First Declaration makes clear in paragraph 23, and the Second Declaration makes clear at paragraph 24 that,

> Based on my experience, the Weinberger patent does not provide any guidance to one of ordinary skill in the field on how to modify his [pushrod] mechanism to either: (a) associate or disassociate a sample support with a receiving stage; (b) associate or disassociate a sample support with a receiving stage that provides x-y translation; or (c) permit a vacuum lock chamber and an ion source chamber to be in continuous fluid communication while also under a vacuum controlled environment during disassociation, transportation and association of sample supports; as any of these are set forth in Vestal claims 75-87, 90-94, 95, and 97

Appellant submits that Wilhelmi fails to provide one of ordinary skill in the art with a reasonable expectation of successfully producing a sample support transfer mechanism as set forth in claims 75-87, 90-91, 95 and 97. Appellant submits that the illustration and description of a sample filament which remains attached to a pushrod in the ion source is not sufficient to provide one of ordinary skill in the art with a reasonable expectation that they could have modified Wilhelmi to provide a sample support transfer mechanism as set forth in claims 75-87, 90-91, 95 and 97. In support of Appellant's position, Appellant submits the Declarations, and in the particular the facts, reasoning and observations of paragraphs 20-21 in the First Declaration and paragraphs 21-

22 in the Second Declaration, as evidence that Wilhelmi does not describe or suggest a transport mechanism that can disassociate, transport and associate sample supports as set forth in Appellant's claims. Specifically, the First Declaration makes clear in paragraph 21, and the Second Declaration makes clear in paragraph 22, that,

> Based on my experience, the Wilhelmi article provides no description or suggestion to one of ordinary skill in the field of mass spectrometry to associate or disassociate a sample support with a receiving stage, or any guidance to one of ordinary skill in the field on how to modify his mechanism to either associate or disassociate a sample support with a receiving stage.

Appellant submits, and does not believe the Final Office Action asserts otherwise, that neither Duffin, Ledford nor Bakker disclose or suggest any form of sample support transport mechanism or teachings that would provide one of ordinary skill in the art with a reasonable expectation of successfully producing a sample support transfer mechanism as set forth in claims 75-87, 90-91, 95 and 97. In support of Appellant's position, Appellant submits the Declarations, and in the particular the facts, reasoning and observations of paragraph 24 in the First Declaration and of paragraph 25 in the Second Declaration, with respect to Duffin; the facts, reasoning and observations of paragraph 25 in the First Declaration and of paragraph 26 in the Second Declaration, with respect to Ledford; and paragraph 26 in the First Declaration and of paragraph 27 in the Second Declaration, with respect to Bakker.

(7.3.2) Claims 92-94 are patentable under 35 U.S.C. § 103(a)

Appellant respectfully requests reversal of the final rejections, under 35 U.S.C. § 103(a), of claims 92-94, because one of ordinary skill in the art would not have had a reasonable expectation of successfully practicing a method of obtaining mass data comprising at least the steps of:

- disassociating [a] first sample support from [a] sample receiving stage;
- transporting the first sample support from [an] ion source chamber to [a] vacuum lock chamber;
- associating the first sample support with [a] sample support holder;
- disassociating a second sample support from the sample support

holder;

- transporting the second sample support from the vacuum lock chamber to the ion source chamber; [and]
- associating the second sample support with the sample receiving stage.

as set forth in claims 92-94. For the reasons discussed herein with respect to claims 75-87, 90-91 and 95-97, in the context of a sample transport mechanism, the cited references fail to provide one of ordinary skill in the art with a reasonable expectation of successfully practicing the steps of dissociating, transporting, associating of first and second sample supports as set forth in claims 92-94 because the cited references provide no description, suggestion of a mechanism (or method) which could do so or guidance on how to modify the teachings to provide such a mechanism or method.

In support of Appellant's position, Appellant submits the Declarations, and in the particular the facts, reasoning and observations of paragraphs 17-29 in the First Declaration, and paragraphs 17-30 in the Second Declaration, as evidence that one of ordinary skill in the art would not have had a reasonable expectation of successfully modifying and combining two or more of the cited references to produce one or more of claims 92-94 and that such modification and combination would require undue experimentation by one of ordinary skill in the art.

(7.3.3) Claim 93 is further patentable under 35 U.S.C. § 103(a)

Appellant respectfully requests reversal of the final rejections, under 35 U.S.C. § 103(a), of claim 93, because, in addition to the reasons set forth elsewhere herein, one of ordinary skill in the art would not have had a reasonable expectation of successfully practicing at least the steps of claim 92 in combination with the condition,

> wherein the vacuum lock chamber and ion source chamber are in fluid communication and are maintained under a vacuum controlled environment during the dissociating, transporting, and associating of the first and second sample supports.

as set forth in claim 93 (referred to hereafter for the sake of conciseness as "the vacuum controlled environment condition").

Specifically, Appellant submits as set forth elsewhere herein that Beavis does not teach or

suggest a sample support transfer mechanism as set forth in claims 75-87, 90-91, 95 and 97, and does not believe the Final Office Action asserts otherwise. Accordingly, Appellant agrees that Beavis fails to teach a sample support transfer mechanism as set forth in claims 75-87, 90-91, 95 and 97.

As Beavis fails to teach a sample support transfer mechanism, the only mechanism or method remaining for transporting a sample disk into the ion source, or dissociating or attaching of the sample disk to the stepper motor is manual operator intervention. As is clear to one of ordinary skill in the art, the manual performance of such activities cannot be done in a vacuum controlled environment without exposing the operator to the very harmful effects of vacuum. None of Wilhelmi, Weinberger, Duffin, Ledford or Bakker cure this deficiency. Therefore, Beavis can not be said to provide one of ordinary skill in the art with any guidance or reasonable expectation of successfully practicing the vacuum controlled environment condition as set forth in claim 93.

Further, in support of Appellant's position, Appellant also submits the Declarations, and in the particular the facts, reasoning and observations of paragraph 28 in the Second Declaration, as evidence that Beavis does not describe or suggest the vacuum controlled environment condition as set forth in claim 93. Specifically, Prof. Brown in the Second Declaration at paragraph 28 observes,

> Based on my experience, there is no equivalent operator hands-on activity to [the sample transfer steps] while the vacuum lock chamber and the ion source chamber are in continuous fluid communication and under a vacuum controlled environment during disassociation, transportation and association of the sample supports without exposing the operator to the detrimental effects of vacuum.

(emphasis added). The text of Beavis further indicates that the vacuum controlled environment condition as set forth in claim 93 is not met, as set forth elsewhere herein, and that Beavis provides no guidance on practicing this condition, as Prof. Brown observes in the Declarations at paragraph 17,

> the Beavis patent provides no description or suggestion to the practitioner in the field of mass spectrometry of how to load sample disks while under a vacuum controlled environment onto the stepper motor or onto any other device that can move the sample disk [and] the Beavis patent also does not provide any guidance to the practitioner in the field on how to modify his

system to load sample disks under a vacuum controlled environment.

To the extent the Final Office Action asserts that Bakker cures the deficiencies of Beavis when asserting at page 11 of the Final Office Action that Bakker,

> clearly shows that the pump down occurs between the time the sample enters the vacuum lock and the time that the ion source chamber is opened to the vacuum lock chamber for the sample being inserted into the ion source chamber. From this is clear that the Beavis reference discussion the pump down cannot be used to show that the attachment and detachment of the sample disk to the stepper motor occur either inside or outside of the ion source

Appellant must respectfully disagree for the reasons set forth previously herein.

(7.3.4) Claims 95 and 97 are further patentable under 35 U.S.C. § 103(a)

Appellant respectfully requests reversal of the final rejections, under 35 U.S.C. § 103(a), of claims 95 and 97, because, in addition to the reasons set forth elsewhere herein, one of ordinary skill in the art would not have had a reasonable expectation of successfully producing a "sample support transfer mechanism" in combination with a

> means for maintaining the vacuum lock chamber and the ion source chamber in fluid communication and under a vacuum controlled environment during disassociation, transportation and association of the first and second sample supports.

as set forth in claims 95 and 97 (referred to hereafter for the sake of conciseness as "the vacuum controlled environment limitation").

Appellant submits that Beavis does not teach or suggest a sample support transfer mechanism as set forth in claims 75-87, 90-91, 95 and 97, and does not believe the Final Office Action asserts otherwise. Accordingly, Appellant agrees that Beavis fails to teach a sample support transfer mechanism as set forth in claims 75-87, 90-91, 95 and 97.

As Beavis fails to teach a sample support transfer mechanism, the only mechanism remaining for the transporting a sample disk into the ion source, or dissociating or attaching of the sample disk to the stepper motor is manual operator intervention. As is clear to one of ordinary skill in the art, the manual performance of such activities cannot be done in a vacuum controlled environment without exposing the operator to the very harmful effects of vacuum.

None of Wilhelmi, Weinberger, Duffin, Ledford or Bakker cure this deficiency. Therefore, Beavis can not be said to teach or suggest the vacuum controlled environment limitation as set forth in claims 95 and 97.

> Further, in support of Appellant's position, Appellant also submits the Declarations, and in the particular the facts, reasoning and observations of paragraph 28 in the Second Declaration, as evidence that Beavis does not describe or suggest the vacuum controlled environment limitation as set forth in claims 95 and 97. Specifically, Prof. Brown in the Second Declaration at paragraph 28 observes, Based on my experience, there is no equivalent operator hands-on activity to [the sample support transfer mechanism] while the vacuum lock chamber and the ion source chamber are in continuous fluid communication and under a vacuum controlled environment during disassociation, transportation and association of the sample supports without exposing the operator to the detrimental effects of vacuum.

(emphasis added).

The text of Beavis further indicates that the vacuum controlled environment condition as set forth in claims 95 and 97 is not met, as set forth elsewhere herein, and that Beavis provides no guidance on practicing this condition, as Prof. Brown observes in the Declarations at paragraph 17,

> the Beavis patent provides no description or suggestion to the practitioner in the field of mass spectrometry of how to load sample disks while under a vacuum controlled environment onto the stepper motor or onto any other device that can move the sample disk [and] the Beavis patent also does not provide any guidance to the practitioner in the field on how to modify his system to load sample disks under a vacuum controlled environment.

To the extent the Final Office Action asserts that Bakker cures the deficiencies of Beavis when asserting at page 11 of the Final Office Action that Bakker,

> clearly shows that the pump down occurs between the time the sample enters the vacuum lock and the time that the ion source chamber is opened to the vacuum lock chamber for the sample being inserted into the ion source chamber. From this is clear that the Beavis reference discussion the pump down cannot be used to show that the attachment and detachment of the sample disk to the stepper motor occur either inside or outside of the ion source

Appellant must respectfully disagree for the reasons set forth previously herein.

(7.4) The Final Office Action Fails to Establish a Motivation to Combine

The burden is on the examiner to "support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." Ex parte Clapp, 227 USPQ at 973; MPEP § 706.02 (j) (8th Ed., Revision No. 2, May 2004). The reasoning supporting a suggestion or motivation to combine references must show how one of ordinary skill in the art, with no knowledge of the claimed invention, would be motivated to produce the claimed invention as a whole. See Graham, 383 U.S. at 17-18, 148 USPQ at 467; In re Rouffet, 149 F.3d at 1357, 47 USPQ2d at 1457, 1458; In re Vaeck, 947 F.2d at 493, 20 USPQ2d at 1442. To establish that the requisite suggestion or motivation to combine exits, there must be a clear and particular showing that the prior art would have suggested to one of ordinary skill in the art that they should make the claimed device or process. See In re Rouffet, 149 F.3d at 1357, 47 USPQ2d at 1457, 1458; In re Vaeck, 947 F.2d at 493, 20 USPQ2d at 1442.

In addition, it is well settled that the motivation to combine must show how one of ordinary skill in the art would combine the teachings to produce the claimed invention as a whole. See In re Rouffet, 149 F.3d at 1357, 47 USPQ2d at 1457, 1458; Gillette, 919 F.2d at 724, 16 USPQ2d at 1927. Establishing that every element of a claimed invention is found in the prior art is not sufficient, what must be established is motivation to provide the claimed combination. See id.

A determination of whether a motivation to combine exists necessarily requires, among other things, an evaluation of the state of art and the reading one of ordinary skill in the art would have given to references in the prior art. See Graham., 383 U.S. at 17-18, 148 USPQ at 467; In re Rouffet, 149 F.3d at 1357, 47 USPQ2d at 1457, 1458; Gillette, 919 F.2d at 724, 16 USPQ2d at 1927; In re Vaeck, 947 F.2d at 493, 20 USPQ2d at 1442. The usual way of determining the ordinary skill in the art is with reference to the subjective reaction of a person who was familiar with and practiced the art at the time the invention was made. See, In re Meng, 1492 F.2d at, 848-49,181 USPQ at 98; see also In re Oerlich, 579 F.2d at 91, 198 USPQ at 215. First hand

practical knowledge of and familiarity with the art at the time of the invention, by an expert, is probative evidence of the state of the art and ordinary skill in the art at the time of the invention. See, In re Piasecki, 745 F.2d at 1473, 223 USPQ at 789.

Prof. Brown has first hand practical knowledge of and familiarity with both the art and its practitioners of ordinary skill at the time of the invention, as well as practical hands-on experience in the development of mass spectrometry instrumentation. See, e.g., the Declarations at paragraphs 2 and 3. Prof. Brown has evaluated the cited references and explicitly described the one of ordinary skill in the art on which his evaluations are based. See, e.g., the Declarations paragraphs 6 and 7; and the Second Declaration at paragraph 13. The Final Office Action nowhere challenges Prof. Brown's description of one of ordinary skill in the art or provides an alternative description. Accordingly, the observations and views of Prof. Brown, as one with particular contemporaneous knowledge of the art and those of ordinary skill in it, are probative evidence on the issue of the suggestions or motivations the art, the nature of the problem to be solved and the cited references would provide to one of ordinary skill in the art. See, In re Piasecki, 745 F.2d at 1473, 223 USPQ at 789. Thus, the observations and views of Prof. Brown are probative evidence on the issue of motivation to combine. See, id.

The Final Office Action asserts that multiple sections of Beavis, as well as the problem of which the cited references are concerned, would motivate one of ordinary skill in the art to combine the cited references to produce Appellant's claims 75-87, 90-94, 95 and 97 as a whole. (See, Final Office Action at pages 2-3, 4, 8 and 9). Appellant must respectfully disagree with these assertions of the Final Office Action for several reasons. First, the Final Office Action never addresses Appellant's claimed inventions as a whole. Second, the Beavis reference (either alone or in combination with one or more of the cited references) does not motivate one of ordinary skill in the art to combine the cited references to produce any one of Appellant's claims 75-87, 90-94, 95 and 97 as a whole.

The Final Office Action fails to address Appellant's claimed inventions as a whole when rejecting claims 75-87, 90-94, 95 and 97 as obvious over the cited references. The Final Office Action provides no particular showing or reasoning of motivation to produce Appellant's claimed invention; rather, the Final Office Action broadly concludes that because production of an "automated system" would be obvious, so to would Appellant's claimed invention. Such

reasoning is facially insufficient to establish a *prima facie* case of obviousness because it does not address Appellant's claimed invention, limitation by limitation and as a whole, but rather addresses a generalization, or gist, of the invention. See In re Rouffet, 149 F.3d at 1357, 47 USPQ2d at 1457, 1458; Gillette, 919 F.2d at 724, 16 USPQ2d 1at 1927; see also MPEP § 2141.02 (8th Ed., Revision No. 2, May 2004). To establish a *prima facie* case of obviousness requires that each claimed invention be evaluated as a whole. See id. Focusing on a concept or gist of a claimed invention is a legally improper way to simplify the difficult determination of obviousness. See id.

Specifically, the Final Office Action distills Appellant's appealed claims down to a concept -automation of a mass spectrometer- and proceeds to evaluate Appellant's claimed inventions by determining whether automation of a mass spectrometer, instead of the claims as a whole, is motivated by the prior art. Although the nature of the problem to be solved can provide a motivation to combine, it can not be used as a gloss to cover substantive gaps in the obviousness case. Al-Site, 174 F.3d at 1324, 50 USPQ2d at 1171; Ryko Mfg. Co. v. Nu-Star, Inc., 950 F.2d 714, 718, 21 USPQ2d 1053, 1057 (Fed. Cir. 1991).

The Final Office Action asserts that Beavis provides a motivation to combine the cited references because Beavis mentions that automation is an object of his invention. However, the Final Office Action fails to set forth particular findings on how each claim as a whole is rendered obvious by this. In fact, the Final Office Action repeatedly grounds its assertion that the requisite motivation to combine on the appearance in the cited references of an automation concept. In particular, the Final Office Action asserts these grounds repeatedly as follows:

- asserting at page 2 that motivation to combine exists because Beavis at column 3, lines 19-23, states, "It is further an object of the present invention to provide an instrument and method which are relatively simple to operate, relatively low cost, and which may be automated to sequence thousands of gene bases per hour." (emphasis in the Final Office Action)

- asserting at page 3 that motivation to combine exists because, "This section [col. 3, lines 19-23 of Beavis] teaches that automation will allow the sequencing of thousands of gene bases per hour of analysis. This automation is not limited to any specific types by the language of this section.";

- asserting at page 4 that that motivation to combine exists because, "Beavis clearly teaches automation of two parts of the analysis process";
- asserting at page 8 again that motivation to combine exists because Beavis states col. 3, lines 19-23 "which may be automated" at col. 3, lines 19-23 of Beavis and (emphasis in the Final Office Action);
- asserting at page 9 that, "One recognized reason for motivation that is important to the instant combination is the references are solving a similar problem. It s in this context that the discussion of automation is important...In particular the Wilhelmi references are concerned with the total automation of a manual mass spectrometric analysis process...".

Instead of being a starting point for assessing whether a motivation to combine exists with respect to one or more of Appellant's claims, the concept of automation appears to be the entire basis for the Final Office Action's conclusion that Beavis teaches or suggests combining the cited references to provide Appellant's claimed inventions. The Final Office Action's repeated characterization and discussion of motivation to combine as simply the concept of automation ignores Appellant's claims as a whole. See Al-Site, 174 F.3d at 1324, 50 USPQ2d at 1171; In re Rouffet, 149 F.3d at 1357, 47 USPQ2d at 1457, 1458; Ryko, 950 F.2d at 718, 21 USPQ2d at 1057; Gillette, 919 F.2d at 724, 16 USPQ2d at 1927; see also MPEP § 2141.02 (8th Ed., Revision No. 2, May 2004).

Whether Beavis teaches that automation is an object of his application is also not determinative of whether the requisite motivation to combine the cited references exists, either in Beavis or in the knowledge generally available in the art, because Appellant's claimed inventions are not merely the automation of a manual activity. See In re Rouffet, 149 F.3d at 1357, 47 USPQ2d at 1457, 1458; Gillette, 919 F.2d at 724, 16 USPQ2d at 1927; see also MPEP § 2141.02 (8th Ed., Revision No. 2, May 2004). The Final Office Action's implicit reduction of Appellant's claimed inventions to a simple category, or gist, and then setting forth reasons and showing why this gist is obvious has no bearing on whether any claim, as a whole, is obvious. As a result, the Final Office Action's failure to address the limitations of the claims and each claim as a whole is legally improper and can not support or establish a *prima facie* case of obviousness against

Appellant's claimed inventions. See id.

The Final Office Action purportedly relies upon multiple passages in Beavis for the conclusion that Beavis "teaches two specific types of automation –sample preparation and sample introduction into the mass spectrometer" citing "the detailed description following the statement of objectives in the patent." Appellant must disagree. Beavis simply does not support this reading. The detailed description following the statement of the objectives, supposedly columns 3 and 4, describes, as Beavis himself makes clear, that what he means by automated versus manual loading refers to loading samples onto the disk. For example, Beavis describes at column 4, lines 42-43, that: "Fig. 1 depicts a suitable automated DNA sample preparation and loading technique." (emphasis added). Fig. 1 depicts an automated approach to sample preparation followed by spotting on the disk. This is clearly what Beavis refers to at column 5, lines 5-18, and at the end of the paragraph spanning columns 4-5 where he states: "The technique of the present invention does not... require the full time attention of a dedicated, trained operator to prepare and load the samples."

Further, the time savings Beavis purports to provide with his invention in columns 1-5, relate to using mass spectrometry instead of gel electrophoresis to analyze a sample. (See also, Beavis, Background of the Invention, where Beavis clearly purports to provide a technique faster than gel electrophoresis methods). Nowhere does Beavis suggest that time savings are to be obtained by automation of disk insertion. Rather, all the time savings referred to in Beavis refer either to those provided by mass spectrometry versus gel electrophoresis or the automation of sample preparation and loading onto disks. Thus, the phrase "Even if the samples were manually loaded..." refers to sample loading onto a disk, not to disk insertion into the mass spectrometer.

Further, the Final Office Action's position that "Beavis uses the words "loaded" or "load" in two places where it could refer to either or both of these the above uses (see column 5, lines 5-10 and 14-18)" is not a reading supported by the context of these passages. In these passages there is only one consistent reading, Beavis refers to the loading of samples onto a disk. Column 5, lines 5-18 are the end of the section in Beavis describing Figure 1. Fig. 1 depicts an automated approach to sample preparation followed by spotting on the disk. This is clearly what Beavis refers to at column 5, lines 5-18, and where he states: "The technique of the present invention does not... require the full time attention of a dedicated, trained operator to prepare and

load the samples."

In particular, the paragraph spanning columns 4-5 (column 4, line 63, to column 5, line 18), reads as follows:

> Once the samples in suitable matrix are deposited on the disk, the disk may be inserted into the ion source of a mass spectrometer through the vacuum lock. Any gas introduced in this procedure must be removed prior to measuring the mass spectrum. Loading and pump down of the spectrometer typically requires two to three minutes, and the total time for measurement of each sample to obtain a spectrum is typically one minute or less. Thus 50 or more complete DNA spectrum may be determined per hour according to the present invention. Even if the samples were manually loaded, as disclosed is copending U.S. Pat. application Ser. No. 07/413,321 filed Sept. 27, 1989 and hereby incorporated by reference, less than one hour would be required to obtain sequence data on a particular segment of DNA, which might be from 400 to 600 bases in length. Even this latter technique is much faster than the conventional DNA sequencing techniques, and compares favorably with the newer automated sequencers using fluorescence labeling. The technique of the present invention does not, however, require the full-time attention of a dedicated, trained operator to prepare and load the samples, and preferably is automated to produce 50 or more spectrum per hour.

The context of the paragraph for the passages at column 5, lines 5-18, makes clear that the term "loaded" when used with the term "samples" in the paragraph refers to the loading of samples onto the disk (for example by spotting) not the insertion of the disk into the ion source region or onto the other stepper motor (item number **28**) for at least the facts and reasons of paragraphs 17-19 in the First Declaration, Paragraphs 17-20 in the Second Declaration, and the following five reasons.

First, the passage refers to the loading of a sample, not the disk. When describing the loading of the mass spectrometer Beavis repeatedly refers to this as loading the disk, and when Beavis describes the loading of samples repeatedly refers to the loading them onto the disk. The single occurrence at column 2, lines 55-59, "each of these collections [fragments of DNA] is sequentially loaded into an ultraviolet laser desorption mass spectrometer, and the mass spectrum of each collection is recorded and stored in the memory of a computer." does not change this usage and neither does this sentence at column 2 hint or suggest that the "sequential loading" is to automated. Rather, this sentence immediately follows and is followed by a comparison of the

advantages of a mass spectrometric based DNA sequencing technique to the far slower gel electrophoresis method.

Second, Beavis at column 5, lines 5-10, makes no reference to insertion of a disk, these lines read: "Even if the samples were manually loaded, as disclosed in copending U.S. Pat. application Ser. No. 07/413,321 filed Sept. 27, 1989 and hereby incorporated by reference, less than one hour would be required to obtain sequence data on a particular segment of DNA, which might be from 400 to 600 bases in length."

Third, column 5, lines 5-10 contrasts itself with the manual loading disclosed in USSN 07/413,32, issued as U.S. Patent No. 5,045,694 ("the '694 patent"). The only direct mention of sample loading in the '694 patent refers to loading of sample on a probe tip, specifically the '694 patent at column 6, lines 29-31 states: "With a typical sample loading of 0.1-20 p mol of analyte on the probe tip (3 mm^2) good signals were observed." (emphasis added). Moreover, the portion of the '694 patent cited in the Final Office Action at page 8 (column 4, lines 4-9) reads: "The probe **10** is manually inserted and may be manually removed from the round bore **12** of the metal wall **13** of the spectrometer"; makes no reference to sample loading and thus cannot be what column 5, lines 5-10 of Beavis is contrasting itself with. The Final Offices Action's assertions to the contrary are simply unfounded.

Fourth, Beavis himself makes clear that what he means by automated versus manual loading refers to loading samples onto the disk. For example, Beavis describes at column 4, lines 42-43, that: "Fig. 1 depicts a suitable automated DNA sample preparation and loading technique." (emphasis added). Fig. 1 depicts an automated approach to sample preparation followed by spotting on the disk. This is clearly what Beavis refers to at column 5, lines 5-10, and at the end of the paragraph spanning columns 4-5 where he states: "The technique of the present invention does not... require the full time attention of a dedicated, trained operator to prepare and load the samples."

Fifth, the time savings Beavis purports to provide with his invention in columns 1-5, relate to using mass spectrometry instead of gel electrophoresis to analyze a sample. (See also, Beavis, Background of the Invention, where Beavis clearly purports to provide a technique faster than gel electrophoresis methods). Nowhere does Beavis suggest that time savings are to be

obtained by automation of disk insertion. Rather, all the time savings referred to in Beavis refer either to those provided by mass spectrometry versus gel electrophoresis or the automation of sample preparation and loading onto disks. Thus, the phrase "Even if the samples were manually loaded..." refers to sample loading onto a disk, not to disk insertion into the mass spectrometer.

Although, the Final Office Action appears to rely on multiple other passages in Beavis[3] as the basis for the conclusion that Beavis suggests automation of disk insertion and attachment, none of these instances when read in proper context support the conclusion that Beavis suggests automating sample introduction into the mass spectrometer. For example, despite the Final Office Actions assertions to the contrary, there is no ambiguity in the use of the terms "load" or "loaded" at column 5, lines 5-18, or anywhere else in Beavis that would support the position that Beavis suggests automating sample introduction into the mass spectrometer. Besides the assertion of a non-existent ambiguity, the only reasoning the Final Office Action sets forth, to support the proposition that that Beavis suggests automating sample introduction into the mass spectrometer, is based on the paragraph spanning columns 4-5 and column 5, lines 5-18, clearly do not support this reading as described previously and above.

Appellant respectfully submits that the burden is on the Examiner to establish the requisite motivation to combine. Ex parte Clapp, 227 USPQ at 973; MPEP § 706.02 (j) (8th Ed., Revision No. 2, May 2004). This burden cannot be met by vague reference to what terms might mean in a reference or by reasoning that because a reference does not explicitly preclude a specific meaning it must be suggested. See In re Rouffet, 149 F.3d at 1357, 47 USPQ2d at 1457-58; In re Vaeck, 947 F.2d at 493, 20 USPQ2d at 1442. Rather, there must be a clear and particular showing that the prior art would have suggested to one of ordinary skill in the art that they should make the claimed device or process as a whole. See id. This the Final Office Action has not done in view of the reasons set forth herein and the Declarations of Prof. Brown. Therefore, Appellant respectfully submits that the Final Office Action fails to establish a *prima*

[3] Specifically, the Final Office Action appears to rely at least on: (i) the background section of columns 1 and 2; (ii) column 1, lines 58-61; (iii) column 2, lines 55-59; (iv) the list of objectives at column 3, lines 19-23; (v) column 4, lines 42-62; (vi) column 4 line 67 to column 5, line 2; (vii) column 5, lines 5-18; and (viii) column 5, lines 24-28. Appellant submits that all of these instances where previously considered by Prof. Brown as he reviewed the entirety of Beavis as well as US Patent 5,045,694 (see, e.g., the Declarations paragraphs 6 and 7) and by Applicant. As Applicant expressly stated at page 7, in the Reply of March 8, 2004, and Appellant again states, "[n]owhere does Beavis suggest that time savings are to be obtained by automation of disk insertion."

facie case that one of ordinary skill in the art would have had a motivation to combine the cited references to produce any of the inventions in Appellant's claims 75-87, 90-94, 95 and 97 as a whole. See Graham, 383 U.S. at 17-18, 148 USPQ at 467; In re Rouffet, 149 F.3d at 1357, 47 USPQ2d at 1457, 1458; Gillette, 919 F.2d at 724, 16 USPQ2d at 1927; In re Vaeck, 947 F.2d at 493, 20 USPQ2d at 1442.

(7.4.1) Claims 75-87, 90-91, 95 and 97 are patentable under 35 U.S.C. § 103(a)

Appellant respectfully requests reversal of the final rejections, under 35 U.S.C. § 103(a), of claims 75-87, 90-91, 95 and 97, because one of ordinary skill in the art would not have been motivated to modify or combine the cited references to produce any one or more of these claims as a whole. Specifically, neither the cited references themselves nor the knowledge generally available in the art would have suggested to one of ordinary skill in the art to produce a system for obtaining mass data comprising, among other things,

> a sample support transfer mechanism adapted to:
>
> (a) disassociate a first sample support from the sample receiving stage, transport the first sample support from the ion source chamber ...to the vacuum lock chamber and to associate the first sample support with the sample support holder; and
>
> (b) disassociate a second sample support from the sample support holder, transport the second sample support from the vacuum lock chamber ... to the ion source chamber and to associate the second sample support with the sample receiving stage

as set forth in independent claims 75, 90, 95 and 97. As set forth elsewhere herein, Beavis, alone or in combination with the knowledge of the art and one or more of Weinberger, Wilhelmi, Duffin, Ledford, and Bakker, do not teach or suggest a "sample support transfer mechanism," as set forth in Appellant's claims 75-87, 90-91, 95 and 97.

Appellant submits that the art, the nature of the problem to be solved and the cited references do not motivate one of ordinary skill in the art to modify and combine one or more of Beavis, Weinberger, Wilhelmi, Duffin, Ledford, and Bakker to provide a sample support transfer mechanism as set forth in claims 75-87, 90-91, 95 and 97 as a whole. In addition, the Final Office Action does not provide any reasoning, or clear and particular showings related to any one of claims

75-87, 90-91, 95 and 97 as a whole. Instead, the Final Office asserts and reasons that motivation to automate a mass spectrometer renders Appellant's claims obvious. Specifically, the Final Office Action subsumes the limitations of the sample transfer mechanism as set forth in claims 75-87, 90-91, 95 and 97 under automation, and concludes at page 6 that:

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate a vacuum lock connection as taught by Wilhelmi into the Beavis device and method because as shown by Wilhelmi it would have allowed the sample preparation and analysis to occur under condition that would provide further advantages such as time and throughput related to automation. It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the sample cassette as taught by either Wilhelmi or Weinberger and a transport mechanism with a magnetic coupler as taught by Weinberger into the Beavis device because one of ordinary skill in the art would have recognized that having multiple sample trays in the sample chamber would allow the instrument to operate for extended periods without operator interaction and would facilitate the movement of sample trays into and out of the mass spectrometer as shown by Weinberger and Wilhelmi...

without out further particular consideration of the claims as a whole. It is not clear how the elements of the sample support transfer mechanism as set forth in these claims relate to the statements of the Final Office Action because these elements are never discussed. Rather, the Final Office Action substitutes a discussion of the concept of automation for an evaluation of the elements of these claims. As a result, the Final Office Action ignores the claim language and limitations of claims 75-87, 90-91, 95 and 97. As it is well settled that a claims scope and meaning critically turn on the precise words and their order and relationship in the claim, the statements set forth in the Final Office Action fail to address the claims as they are written let alone as a whole. Accordingly, Appellant submits that the Final Office Action fails to establish a motivation to combine the cited references to produce any one or more of claims 75-87, 90-91, 95 and 97.

In support of Appellant's position that the cited references do not provide a motivation to combine the cited or provide a sample transport mechanism as set forth in Appellant's claims 75-87, 90-91, 95 and 97, Appellant also submits the Declarations, and in the particular at least the facts, reasoning and observations of at least: (a) paragraphs 17-19 of the First Declaration and those of paragraphs 17-20 of the Second Declaration, as evidence that Beavis does not provide the motivation to combine; (b) paragraphs 22-23 of the First Declaration and paragraphs 23-24 of

the Second Declaration, as evidence that Weinberger does not provide the motivation to combine; (c) paragraphs 20-21 of the First Declaration and paragraphs 21-22 of the Second Declaration, as evidence that Wilhelmi does not provide the motivation to combine; and (d) paragraphs 24, 25 and 26 of the First Declaration and paragraphs 25, 26, and 27 of the Second Declaration, as evidence that, respectively, Duffin, Ledford, and Bakker do not provide the motivation to combine.

Appellant respectfully submits that the Declarations should be accorded weight on the issue of what Beavis, Weinberger, Wilhelmi, Duffin, Ledford, and Bakker describe and convey to one of ordinary skill in the art. The nature of the matter sought to be established, i.e., the absence of a motivation in the cited references to combine one or more of them to provide a sample support transfer mechanism as set forth in Appellant's claims, is necessarily based on the observations and views of Prof. Brown, as one with particular contemporaneous knowledge of the art and those of ordinary skill in it, because such a matter is the proof of a negative. Nevertheless, to the extent possible, Prof. Brown has made specific reference to the teachings of Beavis (see, e.g., the First Declaration paragraph 19, the Second Declaration paragraphs 19-20), Wilhelmi (see, e.g., the First Declaration paragraph 21, the Second Declaration paragraph 22), Weinberger (see, e.g., the First Declaration paragraph 23, the Second Declaration paragraph 24), and Duffin, Ledford, and Bakker (see, e.g., the First Declaration paragraph 24, 25, 26, the Second Declaration paragraph 25, 26, 27) that demonstrate that the cited references do not provide a motivation to combine the references to provide a sample transport mechanism as set forth in Appellant's claims 75-87, 90-91, 95 and 97.

(7.4.2) Claims 92-94 are patentable under 35 U.S.C. § 103(a)

Appellant respectfully requests reversal of the final rejections, under 35 U.S.C. § 103(a), of claims 92-94, because one of ordinary skill in the art would not have been motivated to modify or combine the cited references to produce any one or more of these claims as a whole. Specifically, neither the cited references themselves nor the knowledge generally available in the art would have suggested to one of ordinary skill in the art to practice a method of obtaining mass data comprising at least the steps of:

- disassociating [a] first sample support from [a] sample receiving

stage;

- transporting the first sample support from [an] ion source chamber to [a] vacuum lock chamber;
- associating the first sample support with [a] sample support holder;
- disassociating a second sample support from the sample support holder;
- transporting the second sample support from the vacuum lock chamber to the ion source chamber; [and]
- associating the second sample support with the sample receiving stage.

as set forth in claims 92-94. As set forth elsewhere herein, Beavis, alone or in combination with the knowledge of the art and one or more of Weinberger, Wilhelmi, Duffin, Ledford, and Bakker, do not teach or suggest a "sample support transfer mechanism," as set forth in Appellant's claims 92-94.

Appellant submits that the art, the nature of the problem to be solved and the cited references do not motivate one of ordinary skill in the art to modify and combine one or more of Beavis, Weinberger, Wilhelmi, Duffin, Ledford, and Bakker to provide sample support transfer steps as set forth in claims 92-94 as a whole. In addition, the Final Office Action does not provide any reasoning, or clear and particular showings related to any one of claims 92-94 as a whole. Instead, the Final Office asserts and reasons that motivation to automate a mass spectrometer renders Appellant's claims obvious. Moreover, in the Final Office Action it is not clear where the sample transfer steps, as set forth in claim 92, are even considered, when it concludes at page 6 that:

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate a vacuum lock connection as taught by Wilhelmi into the Beavis device and method because as shown by Wilhelmi it would have allowed the sample preparation and analysis to occur under condition that would provide further advantages such as time and throughput related to automation. It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the sample cassette as taught by either Wilhelmi or Weinberger and a transport mechanism with a magnetic coupler as taught by Weinberger into the Beavis device because one of ordinary skill in the art would have recognized that having multiple sample trays in the sample chamber would allow the instrument to operate for extended periods without operator interaction and would facilitate the movement of sample trays into and out of the mass spectrometer as shown by Weinberger and

Wilhelmi... (emphasis added)

without out further particular consideration of the claims as a whole. It is not clear how the elements of the sample transfer steps as set forth in these claims relate to the statements of the Final Office Action because these elements are never discussed. Rather, the Final Office Action substitutes a discussion of the concept of automation for an evaluation of the elements of these claims. Further, the Final Office Action simply lumps the method claims and apparatus claims together, failing to acknowledge the differences between these claims. As a result, the Final Office Action ignores the claim language and limitations of claims 92-94. As it is well settled that a claims scope and meaning critically turn on the precise words and their order and relationship in the claim, the statements set forth in the Final Office Action fail to address the claims as they are written let alone as a whole. Accordingly, Appellant submits that the Final Office Action fails to establish a motivation to combine the cited references to produce any one or more of claims 92-94.

In support of Appellant's position that the cited references do not provide a motivation to combine the cited or provide the sample transfer steps as set forth in Appellant's claims 92-94, Appellant also submits the Declarations, and in the particular at least the facts, reasoning and observations of at least: (a) paragraphs 17-19 of the First Declaration and those of paragraphs 17-20 of the Second Declaration, as evidence that Beavis does not provide the motivation to combine; (b) paragraphs 22-23 of the First Declaration and paragraphs 23-24 of the Second Declaration, as evidence that Weinberger does not provide the motivation to combine; (c) paragraphs 20-21 of the First Declaration and paragraphs 21-22 of the Second Declaration, as evidence that Wilhelmi does not provide the motivation to combine; and (d) paragraphs 24, 25 and 26 of the First Declaration and paragraphs 25, 26, and 27 of the Second Declaration, as evidence that, respectively, Duffin, Ledford, and Bakker do not provide the motivation to combine.

Appellant respectfully submits that the Declarations should be accorded weight on the issue of what Beavis, Weinberger, Wilhelmi, Duffin, Ledford, and Bakker describe and convey to one of ordinary skill in the art. The nature of the matter sought to be established, i.e., the absence of a motivation in the cited references to combine one or more of them to provide the sample transfer steps as set forth in Appellant's claims 92-94, is necessarily based on the observations and views of Prof. Brown, as one with particular contemporaneous knowledge of

the art and those of ordinary skill in it, because such a matter is the proof of a negative. Nevertheless, to the extent possible, Prof. Brown has made specific reference to the teachings of Beavis (see, e.g., the First Declaration paragraph 19, the Second Declaration paragraphs 19-20), Wilhelmi (see, e.g., the First Declaration paragraph 21, the Second Declaration paragraph 22), Weinberger (see, e.g., the First Declaration paragraph 23, the Second Declaration paragraph 24), and Duffin, Ledford, and Bakker (see, e.g., the First Declaration paragraph 24, 25, 26, the Second Declaration paragraph 25, 26, 27) that demonstrate that the cited references do not provide a motivation to combine the references to provide the sample transfer steps as set forth in Appellant's claims 92-94.

(7.4.3) Claim 93 is further patentable under 35 U.S.C. § 103(a)

Appellant respectfully requests reversal of the final rejections, under 35 U.S.C. § 103(a), of claim 93, because one of ordinary skill in the art would not have been motivated to modify or combine the cited references to produce this claim as a whole. Specifically, neither the cited references themselves nor the knowledge generally available in the art would have suggested to one of ordinary skill in the art to practice a method of obtaining mass data comprising at least the steps of claim 92 in combination with the condition,

> wherein the vacuum lock chamber and ion source chamber are in fluid communication and are maintained under a vacuum controlled environment during the dissociating, transporting, and associating of the first and second sample supports.

as set forth in claim 93.

Appellant submits that the art, the nature of the problem to be solved and the cited references do not motivate one of ordinary skill in the art to modify and combine one or more of Beavis, Weinberger, Wilhelmi, Duffin, Ledford, and Bakker to practice the vacuum controlled environment condition as set forth in claim 93 as a whole. In addition, the Final Office Action does not provide any reasoning, or clear and particular showings related to claim 93 as a whole. Instead, the Final Office asserts and reasons that motivation to automate a mass spectrometer renders Appellant's claims obvious. Moreover, in the Final Office Action it is not clear where the vacuum controlled environment condition as set forth in claim 93 is even considered, when it concludes at page 6 that:

> It would have been obvious to one of ordinary skill in the art at the time the

> invention was made to incorporate a vacuum lock connection as taught by Wilhelmi into the Beavis device and method because as shown by Wilhelmi it would have allowed the sample preparation and analysis to occur under condition that would provide further advantages such as time and throughput related to automation. It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the sample cassette as taught by either Wilhelmi or Weinberger and a transport mechanism with a magnetic coupler as taught by Weinberger into the Beavis device because one of ordinary skill in the art would have recognized that having multiple sample trays in the sample chamber would allow the instrument to operate for extended periods without operator interaction and would facilitate the movement of sample trays into and out of the mass spectrometer as shown by Weinberger and Wilhelmi... (emphasis added)

without out further particular consideration of the claim as a whole. It is not clear how the elements of the vacuum controlled environment condition as set forth in this claim relate to the statements of the Final Office Action because these elements are never discussed. Rather, the Final Office Action substitutes a discussion of the concept of automation for an evaluation of the elements of claim 93. Further, the Final Office Action simply lumps the method claims and apparatus claims together, failing to acknowledge the differences between these claims. As a result, the Final Office Action ignores the claim language and limitations of claim 93. As it is well settled that a claims scope and meaning critically turn on the precise words and their order and relationship in the claim, the statements set forth in the Final Office Action fail to address the claims as they are written let alone as a whole. Accordingly, Appellant submits that the Final Office Action fails to establish a motivation to combine the cited references to produce any one or more of claim 93.

In support of Appellant's position that the cited references do not provide a motivation to combine the cited or provide the vacuum controlled environment condition as set forth in Appellant's claim 93, Appellant also submits the Declarations, and in the particular at least the facts, reasoning and observations of at least: (a) paragraphs 17-19 of the First Declaration and those of paragraphs 17-20 of the Second Declaration, as evidence that Beavis does not provide the motivation to combine; (b) paragraphs 22-23 of the First Declaration and paragraphs 23-24 of the Second Declaration, as evidence that Weinberger does not provide the motivation to combine; (c) paragraphs 20-21 of the First Declaration and paragraphs 21-22 of the Second Declaration, as evidence that Wilhelmi does not provide the motivation to combine; and (d) paragraphs 24, 25 and 26 of the First Declaration and paragraphs 25, 26, and 27 of the Second

Declaration, as evidence that, respectively, Duffin, Ledford, and Bakker do not provide the motivation to combine.

Appellant respectfully submits that the Declarations should be accorded weight on the issue of what Beavis, Weinberger, Wilhelmi, Duffin, Ledford, and Bakker describe and convey to one of ordinary skill in the art. The nature of the matter sought to be established, i.e., the absence of a motivation in the cited references to combine one or more of them to provide the vacuum controlled environment condition as set forth in Appellant's claim 93, is necessarily based on the observations and views of Prof. Brown, as one with particular contemporaneous knowledge of the art and those of ordinary skill in it, because such a matter is the proof of a negative. Nevertheless, to the extent possible, Prof. Brown has made specific reference to the teachings of Beavis (see, e.g., the First Declaration paragraph 19, the Second Declaration paragraphs 19-20), Wilhelmi (see, e.g., the First Declaration paragraph 21, the Second Declaration paragraph 22), Weinberger (see, e.g., the First Declaration paragraph 23, the Second Declaration paragraph 24), and Duffin, Ledford, and Bakker (see, e.g., the First Declaration paragraph 24, 25, 26, the Second Declaration paragraph 25, 26, 27) that demonstrate that the cited references do not provide a motivation to combine the references to provide a the vacuum controlled environment condition as set forth in Appellant's claim 93.

(7.4.4) Claims 95 and 97 are further patentable under 35 U.S.C. § 103(a)

Appellant respectfully requests reversal of the final rejections, under 35 U.S.C. § 103(a), of claims 75-87, 90-91, 95 and 97, because one of ordinary skill in the art would not have been motivated to modify or combine the cited references to produce any one or more of these claims as a whole. Specifically, neither the cited references themselves nor the knowledge generally available in the art would have suggested to one of ordinary skill in the art to produce a system comprising, among other things, a "sample support transfer mechanism" in combination with a

> means for maintaining the vacuum lock chamber and the ion source chamber in fluid communication and under a vacuum controlled environment during disassociation, transportation and association of the first and second sample supports.

as set forth in claims 95 and 97. As set forth elsewhere herein, Beavis, alone or in combination with the knowledge of the art and one or more of Weinberger, Wilhelmi, Duffin, Ledford, and

Bakker, do not teach or suggest a vacuum controlled environment limitation as set forth in Appellant's claims 95 and 97.

Appellant submits that the art, the nature of the problem to be solved and the cited references do not motivate one of ordinary skill in the art to modify and combine one or more of Beavis, Weinberger, Wilhelmi, Duffin, Ledford, and Bakker to provide a vacuum controlled environment limitation as set forth in Appellant's claims 95 and 97 as a whole. In addition, the Final Office Action does not provide any reasoning, or clear and particular showings related to any one of claims 95 and 97 as a whole. Instead, the Final Office asserts and reasons that motivation to automate a mass spectrometer renders Appellant's claims obvious. For example, in the Final Office Action it is not clear where the vacuum controlled environment limitation as set forth in claims 95 and 97 is even considered, when it concludes at page 6 that:

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate a vacuum lock connection as taught by Wilhelmi into the Beavis device and method because as shown by Wilhelmi it would have allowed the sample preparation and analysis to occur under condition that would provide further advantages such as time and throughput related to automation. It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the sample cassette as taught by either Wilhelmi or Weinberger and a transport mechanism with a magnetic coupler as taught by Weinberger into the Beavis device because one of ordinary skill in the art would have recognized that having multiple sample trays in the sample chamber would allow the instrument to operate for extended periods without operator interaction and would facilitate the movement of sample trays into and out of the mass spectrometer as shown by Weinberger and Wilhelmi... (emphasis added)

without out further particular consideration of the claims as a whole. It is not clear how the elements of a vacuum controlled environment limitation as set forth in these claims relate to the statements of the Final Office Action because these elements are never discussed. Rather, the Final Office Action substitutes a discussion of the concept of automation for an evaluation of the elements of these claims. As a result, the Final Office Action ignores the claim language and limitations of claims 95 and 97. As it is well settled that a claims scope and meaning critically turn on the precise words and their order and relationship in the claim, the statements set forth in the Final Office Action fail to address the claims as they are written let alone as a whole. Accordingly, Appellant submits that the Final Office Action fails

to establish a motivation to combine the cited references to produce any one or more of claims 95 and 97.

In support of Appellant's position that the cited references do not provide a motivation to combine the cited or provide the vacuum controlled environment limitation as set forth in Appellant's claims 95 and 97, Appellant also submits the Declarations, and in the particular at least the facts, reasoning and observations of at least: (a) paragraphs 17-19 of the First Declaration and those of paragraphs 17-20 of the Second Declaration, as evidence that Beavis does not provide the motivation to combine; (b) paragraphs 22-23 of the First Declaration and paragraphs 23-24 of the Second Declaration, as evidence that Weinberger does not provide the motivation to combine; (c) paragraphs 20-21 of the First Declaration and paragraphs 21-22 of the Second Declaration, as evidence that Wilhelmi does not provide the motivation to combine; and (d) paragraphs 24, 25 and 26 of the First Declaration and paragraphs 25, 26, and 27 of the Second Declaration, as evidence that, respectively, Duffin, Ledford, and Bakker do not provide the motivation to combine.

Appellant respectfully submits that the Declarations should be accorded weight on the issue of what Beavis, Weinberger, Wilhelmi, Duffin, Ledford, and Bakker describe and convey to one of ordinary skill in the art. The nature of the matter sought to be established, i.e., the absence of a motivation in the cited references to combine one or more of them to provide the vacuum controlled environment limitation as set forth in Appellant's claims 95 and 97, is necessarily based on the observations and views of Prof. Brown, as one with particular contemporaneous knowledge of the art and those of ordinary skill in it, because such a matter is the proof of a negative. Nevertheless, to the extent possible, Prof. Brown has made specific reference to the teachings of Beavis (see, e.g., the First Declaration paragraph 19, the Second Declaration paragraphs 19-20), Wilhelmi (see, e.g., the First Declaration paragraph 21, the Second Declaration paragraph 22), Weinberger (see, e.g., the First Declaration paragraph 23, the Second Declaration paragraph 24), and Duffin, Ledford, and Bakker (see, e.g., the First Declaration paragraph 24, 25, 26, the Second Declaration paragraph 25, 26, 27) that demonstrate that the cited references do not provide a motivation to combine the references to provide a the vacuum controlled environment limitation as set forth in Appellant's claims 95 and 97.

(8) Conclusion

Appellant respectfully submits for the foregoing reasons that claims 75-87, 90-94, 95 and 97 are novel and non-obvious over Beavis, Weinberger, Wilhelmi, Duffin, Ledford, and Bakker, either alone or in proper combination, and that the claims on appeal do not stand or fall together. Specifically, claims 75-87, and 90-91, stand or fall together; claims 92 and 94 stand or fall together; claim 93 stands or falls alone; and claims 95 and 97 stand or fall together. Accordingly, Appellant respectfully requests that the Final Office Action be reversed and the application be passed to issue with claims 75-87, 90-94, 95 and 97 as presented in the Claims Appendix attached hereto.

Dated: January 10, 2005

Respectfully submitted,

By _____

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CLAIMS APPENDIX

75. A system for obtaining mass data comprising:

a mass spectrometer comprising an ion source chamber, wherein the ion source chamber comprises

a sample receiving stage adapted to support a sample support, and

a mechanism to move the sample receiving stage in an x direction and in a y direction perpendicular to the x direction, wherein the x direction and the y direction lie substantially in the same plane;

a laser source in optical communication with the ion source chamber, wherein the laser source is adapted to provide a laser pulse to a sample support in the ion source chamber;

a vacuum lock chamber connected with the ion source chamber, wherein the vacuum lock chamber comprises a sample support holder adapted to support more than one sample support; and

a sample support transfer mechanism adapted to:

(c) disassociate a first sample support from the sample receiving stage, transport the first sample support from the ion source chamber through an output port to the vacuum lock chamber and to associate the first sample support with the sample support holder; and

(d) disassociate a second sample support from the sample support holder, transport the second sample support from the vacuum lock chamber through the output port to the ion source chamber and to associate the second sample support with the sample receiving stage.

76. The system of claim 75 further comprising an electronic control mechanism to control at least the mechanism to move the sample receiving stage.

77. The system of claim 76 wherein the electronic control mechanism comprises a computer.

78. The system of claim 75 wherein the laser source is adapted to provide a laser pulse to irradiate a sample on a sample support.

79. The system of claim 75 wherein the sample support holder comprises a cassette adapted to hold a plurality of sample supports.

80. The system of claim 75 further comprising a sample support.

81. The system of claim 80 wherein the sample support comprises a plurality of samples each disposed at fixed locations on the sample support.

82. The system of claim 81 wherein the sample support further comprises a location identifier associated with at least one of the fixed locations.

83. The system of claim 75 further comprising a door member positioned between the ion source chamber and the vacuum lock chamber.

84. The system of claim 75 further comprising a vacuum pump independently associated with the vacuum lock chamber.

85. The system of claim 75 further comprising a sample preparation system associated with the vacuum lock chamber, wherein the sample preparation system is adapted to deliver a plurality of samples to a sample support prior to introduction to the vacuum lock chamber.

86. The system of claim 85 wherein the sample preparation system comprises a sample loading mechanism adapted to position each of a plurality of liquid samples on a sample support.

87. The system of claim 86 wherein the sample preparation system further comprises a sample curing chamber to dry each of the plurality of liquid samples on a sample support.

90. A system for obtaining mass data comprising:

a mass spectrometer comprising an ion source chamber, wherein the ion source chamber comprises

a sample receiving stage adapted to support a sample support, and a mechanism to move the sample receiving stage;

a laser source in communication with the ion source chamber, wherein the laser source is adapted to provide a laser pulse to a sample support in the ion source chamber;

a vacuum lock chamber connected with the ion source chamber;

a sample storage chamber connected to the vacuum lock chamber, wherein the sample storage chamber comprises a sample support holder adapted to support at least one sample support; and

a sample support transfer mechanism adapted to:

(a) disassociate a first sample support from the sample receiving stage, transport the first sample support from the ion source chamber through an output port to the vacuum lock chamber and to associate the first sample support with the sample support holder; and

(b) disassociate a second sample support from the sample support holder, transport the second sample support from the vacuum lock chamber through the output port to the ion source chamber and to associate the second sample support with the sample receiving stage.

91. The system of claim 90 wherein the mechanism to move the sample receiving stage is adapted to move the sample receiving stage in an x direction and in a y direction perpendicular to the x direction.

92. A method of obtaining mass data comprising the steps of:

supporting each of a plurality of samples at a fixed location on one of a plurality of sample supports;

providing an ion source chamber having a sample receiving stage adapted to support a sample support;

providing a vacuum lock chamber adapted to maintain one or more of the sample supports within a vacuum controlled environment while a sample on another of the sample supports is struck by a laser pulse, wherein the vacuum lock chamber comprises a sample support holder adapted to receive the plurality of sample supports;

moving a first sample support associated with the sample receiving stage within the ion source chamber in an x direction and in a y direction perpendicular to the x direction;

striking with a laser pulse a desired number of the plurality of samples on the first sample support within the ion source chamber to desorb and ionize sample molecules;

disassociating the first sample support from the sample receiving stage;

transporting the first sample support from the ion source chamber to the vacuum lock chamber;

associating the first sample support with the sample support holder;

disassociating a second sample support from the sample support holder;

transporting the second sample support from the vacuum lock chamber to the ion source chamber;

associating the second sample support with the sample receiving stage; moving the second sample support associated with the sample receiving stage within the ion source chamber in an x direction, and in a y direction perpendicular to the x direction; and

striking with a laser pulse a desired number of the plurality of samples on the second sample support within the ion source chamber to desorb and ionize sample molecules.

93. The method of claim 92 wherein the vacuum lock chamber and ion source chamber are in fluid communication and are maintained under a vacuum controlled environment during the dissociating, transporting, and associating of the first and second sample supports.

94. The method of claim 92 further comprising the step of:

recording in a computer mass data corresponding to at least one of the plurality of samples struck with a laser pulse.

95. A system for obtaining mass data comprising:

a mass spectrometer comprising an ion source chamber, wherein the ion source chamber comprises

a sample receiving stage adapted to support a sample support, and a mechanism to move the sample receiving stage in an x direction and in a y direction perpendicular to the x direction, wherein the x direction and the y direction lie substantially in the same plane;

a laser source in optical communication with the ion source chamber, wherein the laser source is adapted to provide a laser pulse to a sample support in the ion source chamber;

a vacuum lock chamber connected with the ion source chamber, wherein the vacuum lock chamber comprises a sample support holder adapted to support more than one sample support;

a sample support transfer mechanism adapted to:

(a) disassociate a first sample support from the sample receiving stage, transport the first sample support from the ion source chamber to the vacuum lock chamber and to associate the first sample support with the sample support holder; and

(b) disassociate a second sample support from the sample support holder, transport the second sample support from the vacuum lock

chamber to the ion source chamber and to associate the second sample support with the sample receiving stage; and

means for maintaining the vacuum lock chamber and the ion source chamber in fluid communication and under a vacuum controlled environment during disassociation, transportation and association of the first and second sample supports.

97. A system for obtaining mass data comprising:

a mass spectrometer comprising an ion source chamber, wherein the ion source chamber comprises

a sample receiving stage adapted to support a sample support, and a mechanism to move the sample receiving stage;

a laser source in communication with the ion source chamber, wherein the laser source is adapted to provide a laser pulse to a sample support in the ion source chamber;

a vacuum lock chamber connected with the ion source chamber; a sample storage chamber connected to the vacuum lock chamber, wherein the sample storage chamber comprises a sample support holder adapted to support at least one sample support;

a sample support transfer mechanism adapted to:

(a) disassociate a first sample support from the sample receiving stage, transport the first sample support from the ion source chamber to the vacuum lock chamber and to associate the first sample support with the sample support holder; and

(b) disassociate a second sample support from the sample support holder, transport the second sample support from the vacuum lock chamber to the ion source chamber and to associate the second sample support with the sample receiving stage; and

means for maintaining the vacuum lock chamber and the ion source chamber in fluid communication and under a vacuum controlled environment during disassociation, transportation and association of the first and second sample supports.

EVIDENCE APPENDIX

581/360 MRD 11-25-9

12-09-1996

100321247

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NOV 25 1996
RECEIPT

To the Honorable Commissioner of Patents and Trade *ments or copy thereof.*

1. Name of conveying party(ies):
Vestec Corporation

Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

3. Nature of conveyance:
☒ Assignment ☐ Merger
☐ Security Agreement ☐ Change of Name
☐ Other _____

Execution Date: November 11, 1996

2. Name and address of receiving party(ies):

Name: PerSeptive Biosystems, Inc.
Street Address: 500 Old Connecticut Path
City: Framingham State: MA
Zip: 01701

Additional name(s) and address(es) attached?
☐ Yes ☒ No

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is: _____

A. Patent Application No. (s)

B. Patent No.(s)
4,731,533 4,958,529 5,498,545 4,766,312
4,999,493 4,902,891 5,015,845 4,883,958
5,160,840

Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Patent Administrator
Testa, Hurwitz & Thibeault, LLP
Street Address: High Street Tower
125 High Street
City: Boston State: MA Zip: 02110

6. Total number of application and patents involved: 9

7. Total fee (37 CFR 3.41) $ 360.00

☒ Enclosed
☐ Authorized to be charged to deposit account

8. Deposit Account Number: 20-0531

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9. Statement of signature.
To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Thomas A. Turano
Name of Person Signing

Signature

11/15/96
Date

Total number of pages comprising cover sheet, attachments and document: 4

431JLC7783/30.274986-1

2 581 360.00 CK

11/25/96 4731533

(7783/30)

ASSIGNMENT

WHEREAS, Vestec Corporation, an entity organized and existing under the laws of the State of Texas (hereinafter "ASSIGNOR"), and having a usual place of business at 9299 Kirby Drive, Houston, Texas 77054, is an owner, free and clear of all encumbrances of right, title and interest in, to and under the patent and patent applications set forth in Appendix A hereto;

WHEREAS, PerSeptive Biosystems, Inc., a corporation organized and existing under the laws of the Commonwealth of Massachusetts, (hereinafter "ASSIGNEE"), having a usual place of business at 500 Old Connecticut Path, Framingham, Massachusetts 01701, is desirous of acquiring the right, title and interest of Vestec Corporation in, to and under said patent and patent applications and the inventions covered thereby;

NOW, THEREFORE, for valuable consideration, the receipt of which is hereby acknowledged, ASSIGNOR does sell, assign, transfer and set over unto said ASSIGNEE, its successors and assigns, its entire right, title and interest in and to all letters patent of the United States and all foreign countries which have been or shall be granted on said patent and patent applications listed on the attached Appendix A, or on said applications, or on any divisionals, continuations, reissues, extensions or other applications based in whole thereon; the same to be held and enjoyed by ASSIGNEE for its own use and enjoyment, and for the use and enjoyment of its successors, assigns or other legal representatives, to the end of the term or terms for which said patents are or may be granted or reissued, as fully and entirely as the same would have been held and enjoyed by ASSIGNOR, if this assignment and sale had not been made; together with all claims for damages by reason of past infringement of said patents, with the right to sue for such damages, and collect the same for its own use and enjoyment, and for the use and enjoyment of its successors, assigns or other legal representatives.

AND, ASSIGNOR agrees for itself and its successors and assigns, with said ASSIGNEE and its successors and assigns, but at the expense and charge of said ASSIGNEE, hereafter to execute all applications, amended specifications, deeds or other instruments, and to do all acts necessary or proper to secure the transfer to the said ASSIGNEE and its successors and assigns of Letters Patent in the United States and all other countries, with specifications and claims to vest and confirm in said ASSIGNEE and its successors and assigns, the legal title to all such patents and to otherwise give full effect to and perfect the rights of said ASSIGNEE under this assignment.

AND, ASSIGNOR does hereby authorize and request competent authorities to issue said Letters Patent as shall be granted upon said applications to said ASSIGNEE and its successors and assigns. ASSIGNOR hereby covenants that it has full right to convey the entire interest herein assigned, and that it has not executed, and will not execute, any agreements inconsistent herewith.

IN WITNESS WHEREOF, the ASSIGNOR has caused this instrument to be executed by its duly authorized officer this 11th day of November, 1996.

Vestec Corporation

BY:: _____
Noubar Afeyan

Title: Chief Executive Officer

Commonwealth of Massachusetts)
County of Middlesex) ss

On this 11th day of November, 1996, before me appeared Noubar Afeyan, to me personally known who, being duly sworn, did depose and say that he is the Chief Executive Officer of Vestec Corporation, the corporation named in and which executed the foregoing instrument; and that said instrument was signed on behalf of said corporation; and said Noubar Afeyan acknowledged said instrument to be the free and authorized act and deed of said corporation.

_____
Notary Public
My Commission Expires: Dec 14, 2001

(7783/30)

Appendix A

ISSUED PATENTS

Patent Number	Issue Date	Country
4,731,533	March 15, 1988	U.S.A.
4,766,312	May 15, 1987	U.S.A.
4,902,891	June 3, 1988	U.S.A.
4,883,958	December 16, 1988	U.S.A.
4,958,529	November 22, 1989	U.S.A.
4,999,493	April 24, 1990	U.S.A.
5,015,845	June 1, 1990	U.S.A.
5,160,840	October 25, 1991	U.S.A.
5,498,545	July 21, 1994	U.S.A.
2,226,882	February 10, 1993	Great Britain

PATENT APPLICATIONS

Application Number	Filing Date	Country
P 39 471 533.3	December 15, 1989	Germany
3 22 770/89	December 14, 1989	Japan

431JLC7783/30.271742-1

ASSIGNMENT

For good and valuable consideration, PERSEPTIVE BIOSYSTEMS, INC., a Delaware corporation and wholly-owned subsidiary of APPLERA CORPORATION, having a place of business located at 500 Old Connecticut Path, Framingham MA 01701, USA (hereinafter referred to as "Assignor"), hereby transfers and assigns to MDS INC., a corporation organized and existing under the laws of the Province of Ontario, Canada, having a place of business located at 100 International Blvd., Toronto, Ontario M9W 6J6, Canada (hereinafter referred to as "Assignee"), through its MDS SCIEX DIVISION, an undivided fifty percent (50%) interest in and to Assignor's right, title, and interest in and to the patents and patent applications listed in Exhibit A to this Assignment, all letters patent which may be granted therefor, and all divisions, reissues, reexaminations, substitutions, continuations, continuations-in-part, foreign counterparts, and extensions of said patents and patent applications (collectively, the "Patents"), together with all rights, including the right of priority provided by the International Convention for the Protection of Industrial Property, claims, actions, and causes of action that Assignor may have against any third party to the extent exclusively related to the Patents, including the right to claim damages for infringement prior to the date hereof of any of such Patents.

Assignor agrees that it will without further consideration, upon request from Assignee to perform such lawful acts, do all such things and execute all such documents as may be necessary or desirable to obtain and maintain such Patents and to vest an undivided fifty percent (50%) interest in title thereto in Assignee, its successors, assigns and legal representatives or nominees.

Assignor hereby authorizes and requests the Commissioner of Patents and Trademarks, and to the corresponding entities or agencies in any applicable foreign countries, to issue to Assignee, the assignee of an undivided fifty percent (50%) interest in the Patents, jointly with Assignor, the right, title and interest in and to such Patents, for their sole use and benefit, and for the use and benefit of their successors and assigns, to the full end of the terms for which Letters Patent may be granted as fully and entirely as the same would have been held by Assignor had this assignment and sale not been made.

WITNESS my hand at Framingham, Massachusetts,

this 22 day of October, 2004.

PERSEPTIVE BIOSYSTEMS, INC.

By: Andrew T. Karnakis

Name: ANDREW T. KARNAKIS

Title: ASST. SECRETARY

STATE OF Massachusetts)
) ss
COUNTY OF Middlesex)

On October 22, 2004 before me, Patricia E. Tocci, personally appeared Andrew T. Karnakis

☑ personally known to me - **OR** - ☐ proved to me on the basis of satisfactory evidence to be the person(s) whose name(s) is/are subscribed to the within instrument and acknowledged to me that he/she/they executed the same in his/her/their authorized capacity(ies), and that by his/her/their signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

WITNESS my hand and official seal.

Patricia E. Tocci
Notary Public in and for said County and State

SAN/100469.1

EXHIBIT A

PATENTS

Cntry	Invention Title	Appl No	Patent Number
US	MASS SPECTROMETER SYSTEM AND METHOD FOR MATRIX-ASSISTED LASER DESORPTION MEASUREMENTS	08/278,405	5,498,545
US	MASS SPECTROMETER SYSTEM AND METHOD FOR MATRIX-ASSISTED LASER DESORPTION MEASUREMENTS	09/038,324	RE37,485
US	IMPROVEMENTS IN TIME OF FLIGHT MASS SPECTROMETRY ANALYSIS OF BIOMOLECULES	08/446,544	5,625,184
US	IMPROVEMENTS IN TIME OF FLIGHT MASS SPECTROMETRY ANALYSIS OF BIOMOLECULES	08/488,127	5,627,369
US	IMPROVEMENTS IN TIME OF FLIGHT MASS SPECTROMETRY ANALYSIS OF BIOMOLECULES	09/058,605	6,002,127
US	IMPROVEMENTS IN TIME OF FLIGHT MASS SPECTROMETRY ANALYSIS OF BIOMOLECULES	09/086,861	6,541,765
US	IMPROVEMENTS IN TIME OF FLIGHT MASS SPECTROMETRY ANALYSIS OF BIOMOLECULES	09/352,246	6,057,543
US	IMPROVEMENTS IN TIME OF FLIGHT MASS SPECTROMETRY ANALYSIS OF BIOMOLECULES	09/527,697	6,281,493
US	IMPROVEMENTS IN TIME OF FLIGHT MASS SPECTROMETRY ANALYSIS OF BIOMOLECULES	08/730,822	5,760,393
US	METHODS AND APPARATUS FOR SEQUENCING POLYMERS WITH A STATISTICAL CERTAINTY USING MASS SPECTROMETRY	08/447,175	5,869,240
US	METHODS AND APPARATUS FOR SEQUENCING POLYMERS USING MASS SPECTROMETRY	08/796,598	5,827,659
US	METHODS AND APPARATUS FOR SEQUENCING POLYMERS USING MASS SPECTROMETRY	08/844,462	5,821,063
US	A TANDEM TIME-OF-FLIGHT MASS SPECTROMETER WITH DELAYED EXTRACTION AND METHOD FOR USE	09/233,703	6,348,688
US	A TANDEM TIME-OF-FLIGHT MASS SPECTROMETER WITH DELAYED EXTRACTION AND METHOD FOR USE	10/023,203	6,770,870
US	A TANDEM TIME-OF-FLIGHT MASS SPECTROMETER WITH DAMPING IN COLLISION CELL AND METHOD FOR USE	09/590,878	6,534,764
US	METHOD AND APPARATUS FOR DETERMINING MOLECULAR WEIGHT OF LABILE MOLECULES	09/579,989	6,504,150
US	PREPARATION OF ION PULSE FOR TIME-OF-FLIGHT AND FOR TANDEM TIME-OF-FLIGHT MASS ANALYSIS	09/546,485	6,545,268
US	PREPARATION OF ION PULSE FOR TIME-OF-FLIGHT AND FOR TANDEM TIME-OF-FLIGHT MASS ANALYSIS	10/356,019	6,670,606
US	A TANDEM TIME-OF-FLIGHT MASS SPECTROMETER WITH IMPROVED MASS RESOLUTION	09/712,882	6,441,369
US	A TANDEM TIME-OF-FLIGHT MASS SPECTROMETER WITH IMPROVED MASS RESOLUTION	10/178,631	6,512,225
US	ROBOTIC SYSTEM HAVING POSITIONALLY ADJUSTABLE MULTIPLE PROBES	10/045,518	6,672,344
US	TANDEM TIME-OF-FLIGHT MASS SPECTROMETER WITH IMPROVED PERFORMANCE DETERMINING MOLECULAR STRUCTURE	10/198,372	6,621,074

PATENT APPLICATIONS

Cntry	Invention Title	Appl. No.	Patent Number
US	MASS SPECTROMETER SYSTEM AND METHOD FOR MATRIX-ASSISTED LASER DESORPTION MEASUREMENTS	09/755,951	
US	IMPROVEMENTS IN TIME OF FLIGHT MASS SPECTROMETRY ANALYSIS OF BIOMOLECULES	10/943,766	
US	HIGH DENSITY SAMPLE HOLDER FOR ANALYSIS OF BIOLOGICAL SAMPLES	10/117,453	
US	A TANDEM TIME-OF-FLIGHT MASS SPECTROMETER WITH DELAYED EXTRACTION AND METHOD FOR USE	10/910,246	
US	PROCESS AND APPARATUS FOR TRANSPORTING SAMPLE PLATES	09/886,734	
US	REMOVABLE HYDROPHOBIC COATING WHICH IMPROVES LIQUID HANDLING PROPERTIES & DETECTION LIMIT OF MALDI TOF INSTRUMENTS	10/227,088	
US	TIME-OF-FLIGHT MASS ANALYZER WITH MULTIPLE FLIGHT PATHS	10/327,471	
US	MALDI PLATE WITH REMOVABLE INSERT	10/683,794	
US	MALDI PLATE WITH REMOVABLE MAGNETIC INSERT	10/683,024	

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Express Mail Label No. ET817713435 US

MJB/jad

PATENT APPLICATION
Attorney Docket No.: SYP-060RECN

UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Marvin L. Vestal		
Application No.:	09/755,951	Art Unit:	1743
Filed:	January 4, 2001	Examiner:	Arlen Soderquist
For:	Mass Spectrometer System and Method for Matrix-Assisted Laser Desorption Measurements		

DECLARATION OF ROBERT S. BROWN UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Sir:

I, Robert S. Brown, hereby declare as follows:

1. I am currently a tenured Associate Professor of Chemistry, Department of Chemistry and Biochemistry, at Utah State University. I have served on the Chemistry and Biochemistry Department faculty since January of 1994. Prior to that I served as an Assistant Professor on the faculty of the Chemistry Department at Colorado State University. I hold a Ph.D. in Chemistry from the Virginia Polytechnic Institute and State University. As a research scientist, I began work in the field of mass spectrometry in 1983. In the past 20 years I have contributed to the development of the mass spectroscopy field in general and matrix assisted laser desorption/ionization (MALDI) mass spectrometers in particular. I have published numerous articles on mass spectroscopy, time-of-flight mass spectroscopy and laser desorption/ionization ion sources for use with mass spectrometers.

2. During my career, I have developed a number of time-of-flight mass spectrometers and mass spectrometry techniques. In particular, I have developed several laser desorption/ionization time-of-flight mass spectrometers and techniques for their use.

3. During my career, I have supervised and served as a thesis advisor to graduate students in doctoral programs at Utah State University and Colorado State University. In addition, I have taught numerous undergraduate and graduate courses in which part of the subject matter concerns mass spectrometry. Also, since 1983 I have regularly attended professional meetings in the field of mass spectrometry. I am therefore familiar with the spectrum of skill levels of workers in the field of mass spectrometry.

4. My experience and education, including a list of publications I have authored, are summarized in my *curriculum vitae*, a true and accurate copy of which is provided with this declaration.

5. Prior to the filing of the present patent application (U.S.S.N. 09/755,951), I was retained as a consultant to Applied Biosystems a Division of Applera Corp. and the successor to PerSeptive Biosystems (hereafter "Applied Biosystems"). I have been compensated for these services at my customary rate of $2,000.00 per day of consultation. It is my understanding that I continue to be retained as a consultant to Applied Biosystems at my customary rate for the present patent application. My compensation for these services is not contingent upon the issuance of the present patent application or outcome of this or any other action.

6. In preparing this declaration, I have reviewed the following documents:

- U.S. Patent No. 5,498,545 issued on March 12, 1996, to Vestal, and reissued as RE37,485 on December 25, 2001 to Vestal.
- A copy of U.S. Application No. 09/755,951 filed on January 4, 2001. ("the Vestal application")
- A copy of the currently pending claims in U.S. Application No. 09/755,951 as of December 5, 2002. ("the Vestal claims" or "the pending claims")
- U.S. Patent No. 5,288,644 issued on February 22, 1994 to Beavis et al. ("the Beavis patent")

- U.S. Patent No. 5,045,694 issued on September 3, 1991 to Beavis et al. ("the'694 patent")
- "An Automatic Analytical Laboratory for Mass-Spectrometric Isotopic-Dilution Analysis of Uranium and Plutonium in Fuel Solutions," Safegaurds Tech., Proc. Symp., 2, pages 165-176 (1970) by Wilhelmi et al. ("the Wilhelmi article")
- U.S. Patent No. 5,382,793 issued on January 17, 1995 to Weinberger et al. ("the Weinberger patent")
- "Automated Sample Transport System for Chromatography/ Secondary Ion Mass Spectrometry" Rev. Sci. Instrum. 60 (6), pages 1071-1074 (1989) by Duffin et al. ("the Duffin article")
- U.S. Patent No. 5,037,611 issued on August 6, 1991 to Ledford ("the Ledford patent")
- "A Direct Insertion Sample handling System for Mass Spectrometers" Int. J. Mass Spectrom. Ion Phys., 3 pages 159-160 (1969) by Bakker and Williams ("the Bakker article")
- the Office Action mailed from the U.S. Patent and Trademark Office on January 24, 2003, for U.S. Application No. 09/755,951 ("the Office Action")

7. My statements in this declaration are based upon my knowledge of the mass spectrometry field, over 20 years of experience with the field and practitioners, and review of the documents listed in paragraph 6. Against this backdrop, I make the following statements of fact and observations.

8. I have been asked to evaluate the references cited in the Office Action. I will refer to the references cited in the Office Action collectively as the cited references. I have also been asked to evaluate the Vestal application and pending claims. In my evaluation, I have been asked to consider the state of the mass spectrometry field as it existed on July 21, 1994. It is my understanding that the present application claims the benefit of July 21, 1994, as its effective filing date.

9. I have considered and been asked to evaluate to what extent, if any, the cited references disclose a system for obtaining mass data having one or more of the following features:

(1) a system having a sample support transfer mechanism adapted to:

disassociate a first sample support from a sample receiving stage, transport the first sample support from an ion source chamber through an output port to a vacuum

lock chamber and to associate the first sample support with a sample support holder; and

disassociate a second sample support from the sample support holder, transport the second sample support from the vacuum lock chamber through the output port to the ion source chamber and to associate the second sample support with the sample receiving stage;

(2) the system of (1) above including a mechanism to move the sample receiving stage in an x direction and in a y direction perpendicular to the x direction, where the x direction and the y direction lie substantially in the same plane;

(3) the system of (1) or (2) above where the system is configured so the vacuum lock chamber and the ion source chamber are in fluid communication and under a vacuum controlled environment during disassociation, transportation and association of the first and second sample supports;

(4) the system of (1), (2), or (3) above where the sample support holder is disposed in the vacuum lock chamber or sample storage chamber;

(5) the system of (1), (2) or (3) above where a sample storage chamber is connected to the vacuum lock chamber; or

(6) the system of (5) above where the sample support holder is disposed in the sample storage chamber.

In evaluating the whether the above systems of (1)-(6) are disclosed in the cited references, I have considered the vacuum lock chamber to be connected with the ion source chamber. I have also evaluated what was described or suggested in the cited references, both separately and together, to the practitioner in the field of mass spectrometry as it existed on July 21, 1994, regarding the use of the systems above to obtain mass data. As a shorthand, I will refer to the support transfer mechanism of (1) above as the "Vestal transfer mechanism".

10. I have also considered and been asked to evaluate to what extent, if any, the cited references disclose a method for obtaining mass data having at least the following steps:

(1) moving a first sample support associated with a sample receiving stage within an ion source chamber in an x direction and in a y direction perpendicular to the x direction;

striking with a laser pulse a desired number of a plurality of samples on the first sample support within the ion source chamber to desorb and ionize sample molecules;

disassociating the first sample support from the sample receiving stage;

transporting the first sample support form the ion source chamber to a vacuum lock chamber;

associating the first sample support with a sample support holder;

disassociating a second sample support from the sample support holder;

transporting the second sample support from the vacuum lock chamber to the ion source chamber;

associating the second sample support with the sample receiving stage;

moving the second sample support associated with the sample receiving stage within the ion source chamber in an x direction, and in a y direction perpendicular to the x direction; and

striking with a laser pulse a desired number of a plurality of samples on the second sample support within the ion source chamber to desorb and ionize sample molecules; or

(2) the method for obtaining mass data including the steps of (1) above in this paragraph where the vacuum lock chamber and ion source chamber are in fluid communication and are maintained under a vacuum controlled environment during the dissociating, transporting, and associating of the first and second sample supports.

I have also evaluated what was described or suggested in the cited references, both separately and together, to the practitioner in the field of mass spectrometry as it existed on July 21, 1994, regarding the use of the steps above to obtain mass data.

11. I have been asked based on my knowledge whether the systems for obtaining mass data as described in the Vestal application and Vestal claims 75-89, 90-91, 95, 96, 97 and 98, when viewed as a whole, was known to the mass spectrometry field, as it existed on July 21, 1994, or that practicing one or more of Vestal claims 75-89, 90-91, 95, 96, 97 and 98 as a whole was recommended by or apparent to the mass spectrometry field.

12. I have also been asked based on my knowledge whether the methods for obtaining mass data as described in the Vestal application and Vestal claims 92-94 when viewed as a whole, was known to the mass spectrometry field, as it existed on July 21, 1994, or that practicing one or more of Vestal claims 92-94 as a whole was recommended by or apparent to the mass spectrometry field.

13. I have reviewed the Vestal application. In particular, I have reviewed the disclosure contained at column 6, line 50, to column 9, line 51 of the Vestal application, Figures 4-7 and the text that describes these Figures. I understand the Vestal application to describe that the sample support holder for holding multiple sample supports, which can be a cassette, can be placed in the vacuum lock chamber. It is my reading that placing the sample support holder in the vacuum lock chamber is not limited to the systems illustrated in Figures 4-7 and that the sample support holder can be placed in the vacuum lock chamber even for those systems that do not have a sample storage chamber. It is my reading that the Vestal application also describes structures and methods that permit the vacuum lock chamber and the ion source chamber to be in fluid communication while also under a vacuum controlled environment during disassociation, transportation and association of first and second sample supports. It is also my reading that methods for obtaining mass data using a sample support holder in the vacuum lock chamber without a sample storage chamber are also described by the Vestal application.

14. In my view and based on my experience with practitioners in the field, upon reading the Vestal application the ordinary practitioner in the field of mass spectrometry would understand that the Vestal application describes systems where a sample support holder can be placed in the vacuum lock chamber even for those systems that do not have a sample storage chamber. In my view and based on my experience with practitioners in the field, upon reading the Vestal application the ordinary practitioner in the field of mass spectrometry would also understand that the Vestal application describes structures and methods that permit the vacuum lock chamber and the ion source chamber to be in fluid communication while also under a vacuum controlled environment during disassociation, transportation and association of sample supports. It is my view that the practitioner with ordinary skill in the field of mass spectrometry would understand that such systems are included in the description at column 6, line 50, to

column 9, line 51 of the Vestal application. It is also my view that the practitioner with ordinary skill in the field of mass spectrometry would understand that methods for obtaining mass data using a sample support holder in the vacuum lock chamber without a sample storage chamber, and methods where the vacuum lock chamber and the ion source chamber are in fluid communication while also under a vacuum controlled environment during disassociation, transportation and association of first and second sample supports, are both described by the Vestal application.

15. I understand the Vestal application to claim and describe various systems that include a transport mechanism configured to transport sample supports to and from an ion source chamber through an output port to a vacuum lock chamber and to associate and dissociate sample supports with a sample support holder and sample receiving stage as discussed in paragraph 9 above. I understand the Vestal application to describe and claim in claims 75-89, 95 and 96 a system that includes a mechanism to move the sample receiving stage in an x direction and in a y direction perpendicular to the x direction, where the x direction and the y direction lie substantially in the same plane. I also understand the Vestal application to describe and claim in claims 90-91, 97 and 98 a system that includes a sample storage chamber connected to the vacuum lock chamber. I further understand the Vestal application to describe and claim in claims 95-98 a system that includes structures configured so that the vacuum lock chamber and the ion source chamber are in fluid communication while also under a vacuum controlled environment during disassociation, transportation and association of the first and second sample supports. In addition, I understand the Vestal application to describe the use of a sample support holder capable of holding multiple sample supports in the vacuum lock chamber or a sample storage chamber. As a shorthand, I will refer to the various systems laid out in Vestal claims 75-89, 90-91, 95, 96, 97 and 98 and as described in the Vestal application collectively as the "Vestal systems."

16. I understand the Vestal application to claim methods for obtaining mass data. I understand from the Vestal application that the methods laid out in claims 92-94 involve using at least the steps of (1) in paragraph 10. I further understand from the Vestal application that the method laid out in claim 93 involves having the vacuum lock chamber and ion source

chamber in fluid communication while also under a vacuum controlled environment during the dissociating, transporting, and associating of the first and second sample supports.
As a shorthand, I will refer to the methods laid out in Vestal claims 92-94 and as described in the Vestal application as the "Vestal methods."

17. I understand the Beavis patent to describe a system where a sample disk is attached directly to the shaft of a stepper motor and the sample disk is then somehow loaded into the ion source through a vacuum lock. However, I can find no description in the Beavis patent that describes how one could either attach or detach the sample disk of Beavis to the stepper motor under a vacuum controlled environment. It is my view that Beavis indicates that attachment and detachment do not occur under a vacuum controlled environment at column 4, lines 65-67, when he instructs that, "any gas introduced in this procedure [the insertion of a disk into the ion source] must be removed prior to measuring the mass spectrum," and at column 5, lines 25-29, where Beavis indicates that pumpdown is required after inserting a new sample disk, "less than five minutes of each two hour period is required for loading and pumpdown." Based on my experience, the Beavis patent provides no description or suggestion to the practitioner in the field of mass spectrometry of how to load sample disks while under a vacuum controlled environment onto the stepper motor or onto any other device that can move the sample disk. Based on my experience, the Beavis patent also does not provide any guidance to the practitioner in the field on how to modify his system to load sample disks under a vacuum controlled environment.

18. I can find no description in the Beavis patent that describes the use of a sample support holder in either a vacuum lock chamber connected with the ion source chamber or a sample storage chamber connected to the vacuum lock chamber. In addition, I can find no description in the Beavis patent that describes a transport mechanism configured to transport sample supports to and from an ion source chamber through an output port to a vacuum lock chamber and to associate and dissociate sample supports with a sample support holder and sample receiving stage as discussed in paragraph 9 above. Based on my experience, the Beavis patent also does not provide any guidance to the practitioner in the field on how to modify his system to include a sample support holder or a transport mechanism as discussed in paragraph 9 above.

19. I have also reviewed the '694 patent which I understand to be the patent which issued from U.S. Patent Application Serial No. 07/413,321 referenced at column 5, lines 6-7 in the Beavis patent. I have been asked to review the '694 patent to place in context the phrase "even if the samples were manually loaded, as disclosed is [sic] copending U.S. Pat. application Ser. No. 07/413,321" appearing at column 5, lines 5-7, in the Beavis patent. The '694 patent does not describe any structure for rotation or x-y translation of the sample probe once inside the ion source. Based on my experience and the lack of any description in the '694 patent of specific probe movement once inside the ion source, I understand and the practitioner in the field of mass spectrometry would understand the text in the Beavis patent on manual and automatic sample loading to be referring to the spotting of samples on the sample disk and not the loading of a sample disk onto a stepper motor.

20. I understand the Wilhelmi article to be concerned with mass spectrometric measurements of uranium and plutonium in nuclear fuel samples placed as solutions onto evaporator filaments (which I subsequently refer to as sample filaments) and dried prior to mass spectrometry analysis. Based on an examination of Figure 3 and its description, Wilhelmi appears to illustrate a system that uses several mechanisms to move a cassette containing beads of nuclear material where each bead is deposited on heating filament. The Wilhelmi system appears to use a mechanism to place the cassette into a preheating chamber and a mechanism is presumably used to move the heated cassette to a lock chamber. A separate pushrod mechanism is used to push a sample filament (referred to as a "bead" in the article) into the ion source where it is vaporized by heating the filament, which appears to also be referred to as an evaporation filament. The vapor that results is then ionized by electrons emitted by the ionization filament in the ion source (electron impact ionization).

21. However, it is my view that the Wilhelmi article does not describe or suggest that the sample filament (or bead) is ever detached from the end of the pushrod (also referred to as a "pinch rod" in the text) during mass spectrometric analysis. It is my view that the sample filament probably does not leave the end of the pushrod based on several parts of the text description. First, the Wilhelmi article does not mention any separate stage to receive a sample filament. Second, the Wilhelmi article states at page 172 that "as soon as the bead is introduced

into the ion source the measurement starts" indicating in my view that the pushrod does not detach from the bead (sample filament) during this step. Third, because there is only one sample filament (sample bead) introduced at a time into the ion source and the sample is vaporized by heating a sample filament, there appears to be no reason to associate the sample filament with a separate stage. Based on my experience, the Wilhelmi article provides no description or suggestion to the practitioner in the field of mass spectrometry to associate or disassociate a sample support with a receiving stage, or any guidance to the practitioner in the field on how to modify his mechanism to either associate or disassociate a sample support with a receiving stage.

22. Making use of the drawing item numbers in the Weinberger patent, I understand the Weinberger patent to describe a system where a shaft (154) is used to pick up a probe tip (30) from a sample ring (152), the probe tip is then pushed into an ion optics region (32) but the probe remains attached to the shaft during mass spectrometric analysis because it is used to rotate the probe tip which contains the sample for analysis. The shaft (154) has o-ring seals (shown in Figure 6), one of which vacuum isolates the ion optics region (32) from the sample chamber (28) containing the sample ring (152) once the ball valve lock (172) is opened and a probe tip has been fully inserted. This o-ring seal prevents fluid communication between the sample chamber (28) and ion optics region (32) by apparently sealing against the ion optic entrance channel (170) when the ball valve lock (172) is opened and the probe tip is fully inserted. The Weinberger patent's structure of a shaft in a channel also prevents x-y translation of the probe during mass spectrometric analysis.

23. It is my view that the Weinberger patent does not describe or suggest a structure that enables a sample support to be dissociated from a transport mechanism and associated with a receiving stage. It is also my view that the structures described and suggested by the Weinberger patent are incompatible with the use of a receiving stage that provides x-y translation because they technically cannot be made to work with such a receiving stage. Based

on my experience, the Weinberger patent does not provide any guidance to the practitioner in the field on how to modify his mechanism to either: (a) associate or disassociate a sample support with a receiving stage; (b) associate or disassociate a sample support with a receiving stage that provides x-y translation; or (c) permit a vacuum lock chamber and an ion source chamber to be in continuous fluid communication while also under a vacuum controlled environment during disassociation, transportation and association of sample supports.

24. I understand the Duffin article to describe a piezoelectric actuated x-y translation stage. However, the Duffin article does not describe or suggest the use of any mechanism that can either transport a sample support to and from an ion source chamber to a vacuum lock chamber or associate and dissociate sample supports with either a sample support holder or sample receiving stage other than via a manual procedure which requires venting to atmosphere the entire instrument. In my view, the Duffin article also does not provide any suggestion or description that would have provided guidance to the ordinary practitioner in the field of mass spectrometry as of July 21, 1994, on how to make or use a mechanism that could transport sample supports to and from an ion source chamber through an output port to a vacuum lock chamber and to associate and dissociate sample supports with a sample support holder and sample receiving stage in a manner equivalent to those described in (1)-(6) in paragraph 9 above.

25. It is my understanding that the Office Action makes reference to the Ledford patent for its use of indicia to provide indexing and sample information. In my view the Ledford patent however does not describe or suggest a mechanism that could transport sample supports to and from an ion source chamber through an output port to a vacuum lock chamber and to associate and dissociate sample supports with a sample support holder and sample receiving stage in a manner equivalent to those described in (1)-(6) in paragraph 9 above.

26. I understand the Bakker article to illustrate a system with a swing butterfly valve but the Bakker article does not describe or suggest the use of any mechanism that can either transport a sample support to and from an ion source chamber to a vacuum lock chamber and associate and dissociate sample supports with a either a sample support holder or sample receiving stage.

While swing butterfly valves and other vacuum isolation methods such as gate valves and ball valves would have been known to practitioners of ordinary skill in the field of mass spectrometry, the Bakker article also does not provide any suggestion or description that would have provided guidance to the ordinary practitioner in the field of mass spectrometry as of July 21, 1994, on how to make or use a mechanism that could transport sample supports to and from an ion source chamber through an output port to a vacuum lock chamber and to associate and dissociate sample supports with a sample support holder and sample receiving stage in a manner equivalent to those described in (1)-(6) in paragraph 9 above.

27. It is my view that while various versions of sample supports, sample holders, sample receiving stages, and mechanisms to hold and move sample supports were known to the mass spectrometry field, as of July 21, 1994, the steps necessary to modify such existing components and produce an instrument in keeping with one or more of the Vestal systems, were not known, and would not have been apparent to an ordinary practitioner in the mass spectrometry field as of July 21, 1994, without the disclosure provided by the Vestal application. Based on my experience, for at least two reasons it would have required extensive experimentation to determine how to modify and then modify existing components to produce a system in keeping with one or more of the Vestal systems. First, absent the Vestal application, the cited references and to my knowledge the mass spectrometry field as of July 21, 1994, provided no working examples of a transfer mechanism such as the Vestal transfer mechanism. Second, absent the Vestal application, the cited references and to my knowledge the mass spectrometry field as of July 21, 1994, provided no guidance on how such existing components could be modified and combined to produce a working instrument for obtaining mass data in keeping with one or more of the Vestal systems.

28. Based on my experience it is my view that, absent the Vestal application, the cited references and to my knowledge the mass spectrometry field as of July 21, 1994, provided no working examples of a method for obtaining mass data in a manner equivalent to those of one or more of the Vestal methods. Based on my experience it is also my view that, absent the Vestal application, the cited references and to my knowledge the mass spectrometry field as of July 21, 1994, provided no description of an instrument or guidance on how to combine

existing structures to produce a working instrument that could be used to obtain mass data in a manner equivalent to that of one or more of the Vestal methods.

29. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the present application or any patent issued in reliance thereon.

Date: 7/22/03

Robert S. Brown

Robert S. Brown, Ph.D.

Express Mail Label No.: ET817713435US

UTAH STATE UNIVERSITY

Curriculum Vitae

DEPARTMENT OF CHEMISTRY AND BIOCHEMISTRY

NAME Robert S. Brown

DATE AND PLACE OF BIRTH June 22, 1956 Medford, Massachusetts

EDUCATION

Ph.D. Analytical Chemistry, Virginia Polytechnic Institute and State University, 1983
B.S. Chemistry, University of Massachusetts at Lowell, 1978

AREAS OF SPECIAL INTEREST

Study of fundamental and applied aspects of mass spectrometry (particularly TOF-MS and FT-MS) of large molecules. Application of mass spectrometry to various chemical problems, with particular emphasis on biochemically relevant systems. Development of laser based ionization methods for mass spectrometry and their application to non-volatile sample characterization. Study of the fundamental processes involved in the matrix assisted laser desorption/ionization (MALDI) process. Synthesis of new MALDI matrix materials. New instrumental designs for TOF-MS. Ion detection processes of large m/z ions. Polymer and biopolymer structural characterization utilizing mass spectrometry.

PROFESSIONAL EXPERIENCE

Associate Professor, Utah State University, 6/98 - Present
Assistant Professor, Utah State University, 1/94 - 6/98
Assistant Professor, Colorado State University, 8/87 - 12/93
Postdoctoral Research Associate, University of Calif., Riverside 8/83 - 6/87

HONORS

Graduation cum laude, University of Lowell, 1978
Research Fellowship, Virginia Polytechnic Institute and State University, 1978-1980
Associate Member, Sigma XI

PROFESSIONAL SOCIETY AFFILIATIONS

American Chemical Society
American Society for Mass Spectrometry
Society for Applied Spectroscopy
Protein Society

UNIVERSITY AND DEPARTMENTAL COMMITTEE ASSIGNMENTS

Graduate Admissions Committee	January 1994 - August 1996
Curriculum Committee	January 1994 - May 1997
Organic Search Committee (Chairman)	June 1995 - January 1996
Building & Space Committee	August 1996 - June 1999
Building & Space Committee (Chairman)	May 1998 - June 1999
Visiting Speakers Committee	May 1997 - June 1998
Graduate Studies Committee	May 1997 - July2001
Graduate Studies Committee (Chairman)	May 1999 - July 2001
P & T Committee - Prof. Lisa Berreau	January 1998 - Present
Advisory & Evaluation Committee	
Dr. Zhihua Shen (Instructor)	September 1999 - June 2001
Departmental Library Committee	May 1999 - 2000
Shimadzu Analytical Laboratory Director	March 2000 - Present
College of Science Dean Search Committee	April 2000 - June 2001
Advisory Committee	June 2000 - Present
Advisory Committee (Chairman)	June 2000 - June 2001
Analytical Search Committee (Chairman)	July 2000 – May 2002
Lab Manager Search Committee	July 2000 - Spring 2001
General Chemistry Steering Committee	July 2000 - Present
P & T Committee - Prof. Tom Chang	January 2000 – Present
P & T Committee - Prof. Phil Silva	September 2002 - Present

TEACHING ASSIGNMENTS (Credits)

Chemistry 761 - Analytical Separations (3)	Spring 1994
Chemistry 780 - Physical-Analytical Seminar (1)	Spring 1994
Chemistry 123 - Principles of Chemistry (3)	Fall 1994
Chemistry 160 - Quantitative Analysis I (2)	Fall 1994
Chemistry 662 - Analytical Chemistry (3)	Spring 1995
Chemistry 160 - Quantitative Analysis I (2)	Spring 1995
Chemistry 780 - Physical-Analytical Seminar (1)	Fall 1995
Chemistry 761 - Analytical Separations (3)	Winter 1996
Chemistry 780 - Physical-Analytical Seminar (1)	Winter 1996
Chemistry 160 - Quantitative Analysis I (2)	Spring 1996
Chemistry 764 - Special Topics in Analytical Chemistry (1)	Spring 1996
Chemistry 360 - Quantitative Analysis II (3)	Fall 1996
Chemistry 361 - Quantitative Analysis Lab (2)	Fall 1996
Chemistry 780 - Physical-Analytical Seminar (1)	Winter 1997
Chemistry 662 - Analytical Chemistry (3)	Spring 1997
Chemistry 764 - Special Topics in Analytical Chemistry (1.5)	Spring 1997
Chemistry 780 - Physical-Analytical Seminar (1)	Fall 1997
Chemistry 121 - Principles of Chemistry (5)	Winter 1998
Chemistry 122 - Principles of Chemistry (4)	Spring 1998
Chemistry 7610 - Chemical Separations (3)	Fall 1998
Chemistry 4990 - Undergraduate Seminar (1)	Fall 1998
Chemistry 7600 - Analytical Spectroscopy (3)	Spring 1999
Chemistry 4990 - Undergraduate Seminar (1)	Spring 1999

Chemistry 4990 - Undergraduate Seminar (1)	Fall 1999
Chemistry 1210 - Principles of Chemistry (4)	Spring 2000
Chemistry 4990 - Undergraduate Seminar (1)	Spring 2000
Chemistry 4990 - Undergraduate Seminar (1)	Fall 2000
Chemistry 7610 - Chemical Separations (3)	Fall 2000
Chemistry 5640 - Instrumental Analysis (3)	Spring 2001
Chemistry 5650 - Instrumental Analysis Lab (2)	Spring 2001
Chemistry 4990 - Undergraduate Seminar (1)	Spring 2001
Chemistry 3600 - Quantitative Chemical Analysis (3)	Fall 2001
Chemistry 3610 - Quantitative Chemical Analysis Lab (1)	Fall 2001
Chemistry 5640 - Instrumental Analysis (3)	Spring 2002
Chemistry 5650 - Instrumental Analysis Lab (2)	Spring 2002
Chemistry 7610 - Chemical Separations (3)	Fall 2002
Chemistry 5640 - Instrumental Analysis (3)	Spring 2003
Chemistry 5650 - Instrumental Analysis Lab (2)	Spring 2003

PROFESSIONAL MEETINGS ATTENDED

Organization	Date	Location
Society of Western Analytical Professors Meeting	Jan. 1988	Pomona, CA
Pittsburgh Conference	Feb. 1988	New Orleans, LA
American Society for Mass Spectrometry Meeting	June 1988	San Francisco, CA
Pittsburgh Conference	March 1989	Atlanta, GA
American Society for Mass Spectrometry Meeting	June 1989	Miami, FL
American Society for Mass Spectrometry Meeting	June 1990	Tucson, AZ
MUACC Meeting	Oct. 1990	Minneapolis, MN
Pittsburgh Conference	March 1991	Chicago, IL
American Society for Mass Spectrometry Meeting	June 1991	Nashville, TN
Rocky Mountain Conference on Analytical Chemistry Meeting	July 1991	Denver, CO
Federation on Analytical Chemistry and Spectroscopy Society Meeting	Oct. 1991	Anaheim, CA
4th Sanibel Conference on Mass Spectrometry	Jan. 1992	Sanibel Island., FL
Pittsburgh Conference	March 1992	New Orleans, LA

PROFESSIONAL MEETINGS ATTENDED (Continued)

American Society for Mass Spectrometry Meeting Desorption'92	June 1992 Sept. 1992	Washington, DC Burg Waldeck, Germany
Organization	Date	Location
Pittsburgh Conference	March 1993	Atlanta, GA
American Society for Mass Spectrometry Meeting	June 1993	San Francisco,
Rocky Mountain Conference on Analytical Chemistry Meeting	August 1993	Denver, CO
Desorption '94	March 1994	Sun River Lodge, OR
1994 Pittsburgh Conference	Feb 27 - Mar 4, 1994	Chicago, IL
42nd American Society for Mass Spectrometry Conference on Mass Spectrometry and Allied Topics	May 29-June3, 1994	Chicago, IL
36th Rocky Mountain Conference on Analytical Chemistry Mass Spectrometry Symposium	Aug 1994	Denver, CO
1995 Pittsburgh Conference	March 6-9,	New Orleans,
43rd American Society for Mass Spectrometry Conference on Mass Spectrometry & Allied Topics	May 1995	Atlanta, GA
37th Rocky Mountain Conference on Analytical Chemistry Mass Spectrometry Symposium	Aug 1995	Denver, CO
1996 Pittsburgh Conference	March 3-8, 1996	Chicago, IL
44th American Society for Mass Spectrometry Conference on Mass Spectrometry and Allied Topics	May 12-16 1996	Portland, OR
38th Rocky Mountain Conference on Analytical Chemistry Mass Spectrometry Symposium	Aug. 1996	Denver, CO
10th Symposium of the Protein Society	Aug. 3-7 1996	San Jose, CA
Desorption '96	Sept. 18-21 1996	Ronne, Denmark

PROFESSIONAL MEETINGS ATTENDED (Continued)

Organization	Date	Location
Eastern Analytical Symposium	Nov. 18-21, 1996	Sommerset, NJ
1997 Pittsburgh Conference	March 16-21, 1997	Atlanta, GA
45th American Society for Mass Spectrometry Conference on Mass Spectrom. & Allied Topics	June 1-5, 1997	Palm Springs, CA
39th Rocky Mountain Conference on Analytical Chemistry Mass Spectrometry Symposium	Aug. 1997	Denver, CO
1998 Pittsburgh Conference	March 1-6, 1998	New Orleans, LA
46th American Society for Mass Spectrometry Conference on Mass Spectrom. & Allied Topics	May 31- June 4, 1998	Orlando, FL
Desorption '98	Sept. 21-26, 1998	Angra dos Reis, Brazil
HPCE Conference	January 24 26, 1999	Palm Springs, CA
1999 Pittsburgh Conference	March 1-6, 1999	Orlando, FL
47th American Society for Mass Spectrometry Conference on Mass Spectrometry & Allied Topics	June 13-18, 1999	Dallas, TX
2000 Pittsburgh Conference	March 1-6, 2000	New Orleans, LA
48th American Society for Mass Spectrometry Conference on Mass Spectrometry and Allied Topics	June 11-15, 2000	Long Beach, CA
Desorption 2000	Sept. 3-8, 2000	St. Malo, France
2001 Pittsburgh Conference	March 4-9, 2001	New Orleans, LA
49th American Society for Mass Spectrometry Conference on Mass Spectrometry and Allied Topics	May 27-31, 2001	Chicago, Il

PROFESSIONAL MEETINGS ATTENDED (Continued)

Organization	Date	Location
2002 Pittsburgh Conference	March 17-22, 2002	New Orleans, LA
50th American Society for Mass Spectrometry Conference on Mass Spectrometry and Allied Topics	June 2-6, 2002	Orlando, FL
Desorption 2002	Sept. 1-5, 2002	Estes Park, CO
Eastern Analytical Symposium	Nov. 18-21 2002	Somerset, NJ

CONFERENCE PRESENTATIONS

Title	Date	Location
"Alternative Approaches to GC/FT-IR/MS"	Feb. 1988	Pittsburgh Conference
"Mass and Infrared Spectrometry Studies of the Laser Desorption Process"	Oct. 1990	Midwest Universities Analytical Chemistry University of Minnesota
"Comparison of Theoretical and Experimental Peakshapes in Matrix Assisted Laser Desorption Mass Spectrometry"	June 1991	ASMS Meeting Nashville, TN
"Improving Ion Transfer and Detection in Matrix Assisted Laser Desorption of High Mass Biomolecules"	Oct. 1991	FACCS Meeting Anaheim, CA
"Cryogenic Trapping of Laser Desorbed Species Coupled with Fourier Transform Infrared Spectrometry"	Oct. 1991	FACCS Meeting Anaheim, CA
"Identification of Matrix Adduct Ion Species in Matrix Assisted Laser Desorption Mass Spectrometry"	Jan. 1992	4th Sanibel Conference on Mass Spectrometry Sanibel Island, FL
"Maximum Likelihood Data Processing Techniques for Improved Mass Resolution in Matrix-Assisted Laser Desorption"	Mar. 1992	Pittsburgh Conference New Orleans, LA
"Adduct Ion formation Pathways in Matrix Assisted Laser Desorption Mass Spectrometry"	June 1992	ASMS Meeting Washington, D.C.

CONFERENCE PRESENTATIONS (Continued)

Title	Date	Location
"Aspects of Large Ion Detection in Matrix Assisted Laser Desorption Mass Spectrometry"	June 1992	ASMS Meeting Washington, D.C.
"Evaluation of an Electrostatic Analyzer Based Time-Of-Flight Mass Spectrometer for Matrix Assisted Laser Desorption"	Sept. 1992	Desorption '92 Burg Waldeck, Germany
"Kinetic Energy Measurements of Matrix Assisted Laser Desorption Generated Ions With an Electrostatic Analyzer Based Time-of-flight Mass Spectrometer"	June 1993	American Society for Mass Spectrometry and Allied Topics Conference San Francisco, CA
"A Postacceleration Detector for Time-of-flight Mass Spectrometry Utilizing Ion to Photon Conversion"	June 1993	American Society for Mass Spectrometry and Allied Topics Conference San Francisco, CA
"Pulsed Ion Extraction at High Accelerating Fields in a MALDI Time-of Flight Mass Spectrometer"	Mar. 1994	Desorption '94 Sun River Lodge, OR
"Pulsed Ion Extraction Combined with High Accelerating Potentials for Matrix-Assisted Laser Desorption Time-of-Flight Mass Spectrometry"	June 1994	42nd American Society for Mass Spectrometry Conf. on Mass Spectrometry and Allied Topics Chicago, IL
"A Comparison of Various Alpha Substituted Cinnamic Acids as Matrices for Matrix-Assisted Laser Desorption"	June 1994	42nd American Society for Mass Spectrometry Conf. on Mass Spectrometry and Allied Topics, Chicago, IL
"Matrix-Assisted Laser Desorption: How Soft an Ionization Process?"	Mar. 1995	1995 Pittsburgh Conference New Orleans, LA
"Hydroxy Benzophenones: A New Class of MALDI Matrices for Proteins/Peptides"	May 1995	43rd American Society for Mass Spectrometry Conf. on Mass Spectrometry and Allied Topics, Atlanta, GA
"Fast Metastable Ion Fragmentation in MALDI"	May 1995	43rd American Society for Mass Spectrometry Conf. on Mass Spectrometry and Allied Topics, Atlanta, GA

CONFERENCE PRESENTATIONS (Continued)

Title	Date	Location
"Matrix Isolation/FT-IR Spectrometry of Laser Desorbed Neutrals"	June 1995	Regional ACS Meeting Park City, UT
"Metastable Ion Decay in Matrix-Assisted Laser/Ionization"	June 1995	Regional ACS Meeting Park City, UT
"Utilization of MALDI In-Source Decay Ions for Peptide/Protein Sequencing"	Mar. 1996	Pittsburgh Conference Chicago, IL
"Early Time Frame Metastable Ion Decay in MALDI"	May 1996	44th ASMS Conference Portland, OR
"Examination Of The Use Of MALDI In-Source Decay For Sequencing Peptides"	May 1996	44th ASMS Conference Portland, OR
"Characteristics Of Several New Alpha Substituted Cinnamic Acids As MALDI Matrices"	May 1996	44th ASMS Conference Portland, OR
"High Mass Resolution MALDI TOF Mass Spectrometry"	Aug. 1996	38th Rocky Mountain Conf. on Analytical Chemistry, Denver, CO
"Utilization of MALDI Fast Metastable Ion Decay Ions for Peptide/Protein Sequencing"	Aug. 1996	10th Protein Society Symposium San Jose, CA
"Factors Influencing Mass Resolution in Delayed Extraction TOF-MS"	Sept. 1996	Desorption '96 Ronne, Denmark
"New Strategies For Protein Sequencing Using MALDI In-Source Decay"	Mar. 1997	Pittsburgh Conference Atlanta, GA
"Synthesis and Utility of Additional Substituted Cinnamic Acid Derivative as MALDI Matrices"	June 1997	45th ASMS Conference Palm Springs, CA
"A New Instrument Design For MALDI Time-of-Flight Mass Spectrometry"	June 1997	45th ASMS Conference Palm Springs, CA
"Protein Sequencing Strategies Based Upon Enzymatic Cleavage and MALDI In-Source Decay"	June 1997	45th ASMS Conference Palm Springs, CA
"IR-MALDI Employing a Short Pulsewidth Nd:YAG Pumped OPO"	March 1998	1998 Pittsburgh Conf. New Orleans, LA

CONFERENCE PRESENTATIONS (Continued)

Title	Date	Location
"Cinnamic Acid Substitution Effects on MALDI Time-of-Flight Mass Spectrometry Performance"	March 1998	1998 Pittsburgh Conf. New Orleans, LA
"Development of New Co-Matrix Systems for MALDI Mass Spectrometry"	June 1998	46th ASMS Conf. Orlando, FL
"Protein Identification Utilizing In-Source Decay MALDI Data Combined With Database Searching"	June 1998	46th ASMS Conf. Orlando, FL
"IR-MALDI Employing a Short Pulsewidth Nd:YAG Pumped OPO"	June 1998	46th ASMS Conf. Orlando, FL
"Metastable Ion Decay of Peptides and Proteins in MALDI TOF-MS Using IR and UV Desorption"	June 1999	47th ASMS Conf. Dallas, TX
"Metastable Ion Decay of Peptides and Proteins in MALDI TOF-MS Using IR and UV Desorption"	June 2000	48th ASMS Conf. Long Beach, CA
"Metastable Ion Decay of Peptides and Proteins in MALDI TOF-MS Using IR and UV Desorption"	June 2000	48th ASMS Conf. Long Beach, CA
"Fragmentation of Peptides/Proteins In MALDI: A Comparison of IR vs. UV Desorption Wavelengths and Positive vs. Negative Ions"	Sept. 2000	Desorption 2000 St. Malo, France
"Optimizing The Extraction Voltage Waveform To Improve The TLF Focussing Of Ions In Delayed Extraction MALDI"	May 2001	49th ASMS Conf. Chicago, IL
"Ionization In MALDI: Do Solvent Occlusions In Matrix Crystals Play A Role?"	June 2002	50th ASMS Conf. Orlando, FL
"Ionization In MALDI, The Role of Trapped Solvent"	Sept. 1-5, 2002	Desorption 2002 Estes Park, CO

INVITED CONFERENCE PRESENTATIONS

Title	Date	Location
"A Comparison of Deconvolution and Maximum Likelihood Data Processing Techniques Applied to Matrix Assisted Laser Desorption Mass Spectra"	July 1991	Rocky Mountain Conference on Analytical Chemistry Denver, CO

INVITED CONFERENCE PRESENTATIONS (continued)

Title	Date	Location
"Evaluation of an Electrostatic Analyzer Based Time-of-flight Mass Spectrometer"	Aug. 1992	34th Rocky Conference on Analytical Chemistry Denver, CO
"Evaluation of Pulsed Ion Extraction at High Accelerating Fields in a MALDI Time-of-flight Mass Spectrometer"	Aug. 1993	35th Rocky Mountain Conference on Analytical Chemistry, Denver, CO
"Low Temperature Matrix Assisted Laser Desorption Mass Spectrometry"	Aug. 1993	35th Rocky Mountain Conference on Analytical Chemistry Denver, CO
"Matrix-Assisted Laser Desorption: How Soft an Ionization Process?	Aug. 1994	36th Rocky Mountain Conference on Analytical Chemistry Denver, CO
"Recent Advances in Matrix Assisted Laser Laser Desorption/Ionization Time-of-Flight Mass Spectrometry"	Aug. 1995	37th Rocky Mountain Conference on Analytical Chemistry Denver, CO
"High Mass Resolution MALDI TOF Mass Spectrometry"	Nov. 1996	Eastern Analytical Symposium Sommerset, NJ
"New Protein Sequencing Strategies Using MALDI In-Source Decay"	Aug. 1997	38th Rocky Mountain Conference on Analytical Chemistry Denver, CO
"IR-MALDI Employing a Short Pulsewidth Nd:YAG Pumped OPO"	Sept. 1998	Desorption 98 Conf. Angra dos Reis,
"Sequencing Peptides and Proteins by In-Source and Post-Source Decay"	Jan. 1999	HPCE Conference Palm Springs, CA
"A Review Of Current Mechanistic Models Of The MALDI Process And Their Implications For Developing Successful Sample Analysis Protocols"	Jan. 2002	Sanibel Island Conf. Sanibel Island, Fl

"Towards a Unified Matrix-Assisted Laser Desorption/Ionization Mechanism: Implications of IR-MALDI Studies"	Nov. 2002	Eastern Analytical Symposium Somerset, NJ

INVITED SEMINARS

Title	Date	Location
"Laser Desorption Mass Spectrometry of Large Molecules"	Nov., 1989	Dept. of Chemistry Tulane University
"Recent Advances in the Mass Spectrometric Analysis of Biological Molecules"	Oct., 1991	Hybritech, Inc. San Diego, CA
"Recent Advances in the Mass Spectrometric Analysis of High Molecular Weight Materials"	April 1991	Sigma Xi CSU
"Recent Development in Matrix Assisted Laser Desorption Mass Spectrometry"	Oct. 1992	Colorado School of Mines
"Utilization of MALDI Fast Metastable Ion Decay Ions for Peptide/Protein Sequencing"	Aug. 1996	Hewlett Packard Co. Palo Alto, CA
"New Developments in MALDI Time-of-flight Mass Spectrometry"	Nov. 1996	University of Georgia
"IR Vs. UV Lasers For Performing Matrix-Assisted Laser Desorption/Ionization: Practical Aspects and Implications For Ionization Mechanisms"	March 2000	Brigham Young U., Provo, UT

FUNDED RESEARCH GRANTS

Title	Donor	Years	Amount
"Study of the Laser Induced Desorption of Non-volatile Material via Matrix Isolation Fourier Transform Infrared Spectrometry"	CSU Faculty Research Grant	1/1/88 - 12/31/88	$ 3,000
Shell Faculty Development Grant	CSU	6/88 - 6/89	$ 10,000
"Laser Induced Thermospray Ionization for Pulsed Mass Spectrometers"	NIH	9/89 - 9/90	$ 33,228

"Laser Desorption Mass Spectrometry: Effects of Various Matrices and Wavelength"	CSU Faculty Research Grant	1/1/90 - 12/31/90	$ 4,300
"Introduction of Gas Chromatography-Mass Spectrometry in the Undergraduate Curriculum"	NSF	1/1/90 - 6/30/91	$ 61,053
"Fundamental Studies of Matrix Assisted Laser Desorption Mass Spectrometry"	NIH	9/30/92 - 2/28/96	$ 296,141
"Frozen Aqueous Matrices For MALDI Mass Spectrometry	USU Faculty Research Grant	7/1/95 - 6/30/96	$ 14,160
"In-Source Decay MALDI TOF-MS of Peptides"	Hewlett Packard Company	1/1/96 - 10/1/97	$ 10,571
"Matrix-Assisted Laser Desorption - Fundamental Studies"	NIH	1/1/97 - 6/30/01	$ 369,774
"Unrestricted Funds for Matrix-Assisted Laser Desorption Studies"	Perseptive Biosystems	6/01/2000	$ 10,000
"Unrestricted Funds for Matrix-Assisted Laser Desorption Studies"	Perseptive Biosystems	1/01/2002	$ 10,000
"Unrestricted Funds for IR-MALDI Development"	Ciphergen Biosystems	11/01/2002	$ 10,000

DONATED EQUIPMENT FOR SUPPORT OF RESEARCH

Instrumentation Received	Donor	Year	Estimated Value
Computer and electronic measurement equipment	Hewlett Packard Company	1996	$ 20,000
Fourier Transform Mass Spectrometer (FTMS 2000)	Phillips Petroleum Co.	1997	$ 350,000
Quadrupole Mass Spectrometer	Phillips Petroleum Co.	1997	$ 25,000
Voyager MALDI TOF-MS	Perseptive Biosystems	8/2002	$ 100,000

RESEARCH PROPOSALS IN PREPARATION

Title	Donor	Years	Amount
"New MALDI TOF-MS Instrument Designs"	NIH	12/1/03-11/30/05	$ 150,000

PLANNED RESEARCH PROPOSALS

"Fundamentals Studies of Matrix-Assisted Laser Desorption/Ionization"	NSF	1/01/04 - 12/31/06	$ 290,000

PUBLICATIONS

1. R.S. Brown, D.W. Hausler and L.T. Taylor, "Gel Permeation Chromatography of Coal Derived Products with On-Line Infrared Detection", *Anal. Chem.* 52, 1511-1515 (1980).

2. R.S. Brown, D.W. Hausler, R.O. Carter and L.T. Taylor, "Fourier Transform Infrared Spectrometric Detection in the Size Exclusion Chromatographic Separation of Polar Synfuel Material" *Anal. Chem.* 53, 197-201 (1981).

3. R.S. Brown, J.W. Hellgeth, D.W. Hausler and L.T. Taylor, "Coal and Coal Products: Analytical Characterization Techniques", *ACS Symposium Series* 205, 163-183 (1982).

4. R.S. Brown and L.T. Taylor, "Speciation of Intermediate Polar Material in Coal Derived Process Solvents by Liquid Chromatography/Fourier Transform Infrared Spectrometry", *Anal. Chem.* 55, 723-730 (1983).

5. R.S. Brown, J.W. Hellgeth, A.M. Squires, and L.T. Taylor, "The Occurrence and Role of Organometallics in Coal Liquefaction", EPRI Report AP-2980, Project 1696-2 (March, 1983).

6. R.S. Brown and L.T. Taylor, "Microbore Liquid Chromatography with Flow Cell Fourier Transform Infrared Spectrometric Detection", *Anal. Chem.* 54, 1492-1497 (1983).

7. D.A. Laude, G.M. Brissey, C.F. Ijames, R.S. Brown and C.L. Wilkins, "Linked Gas Chromatography/Fourier transform Infrared/Fourier Transform Mass Spectrometry with Integrated Electron Impact and Chemical Ionization", *Anal. Chem.* 56, 1163-1168 (1984).

8. J.W. Hellgeth, R.S. Brown and L.T. Taylor, "Effect of Coal Liquefaction Conditions on the trace Element Content of the Soluble Non-Volatile Product", *Fuel* 63, 453-462 (1984).

9. R.S. Brown and L.T. Taylor, "Detectability of Phenols and Amines by Normal Phase Microbore HPLC-FTIR Employing Highly IR Transparent Solvents", *Chromatographia* 18, 396-400 (1984).

PUBLICATIONS (Continued)

10. D.A. Laude, C.L. Johlman, R.S. Brown, C.F. Ijames and C.L. Wilkins, "Pulsed Valve Chemical Ionization for Gas Chromatography/Fourier Transform Mass Spectrometry", *Anal. Chim. Acta* 178 67-77 (1985).

11. R.S. Brown, J.R. Cooper and C.L. Wilkins, "Lightpipe Temperature and Other Factors Affecting Signal in Gas Chromatography-Fourier Transform Infrared Spectrometry", *Anal. Chem.* 57, 2275-2279 (1985).

12. C.L. Johlman, D.A. Laude, R.S. Brown, and C.L. Wilkins, "Pulsed-Valve Reagent Addition for Chemical Ionization Mass Spectrometry: Mass Measurement Accuracy", *Anal. Chem.* 57, 2726-2728 (1985).

13. D.A. Laude, C.L. Johlman, R.S. Brown and C.L. Wilkins, "Negative Chemical Ionization and Accurate Mass Measurement Applications of a linked Gas Chromatography/Fourier transform Infrared Spectrometry/Fourier transform Mass Spectrometer", *Frens. Z. Anal. Chemie* 324, 839-845 (1986).

14. R.S. Brown, D.A. Weil and C.L. Wilkins, "Laser Desorption-Fourier Transform Mass Spectrometry for the Characterization of Polymers", *Macromolecules* 19, 1255-1260 (1986).

15. D.A. Laude, C.L. Johlman, R.S. Brown, D.A. Weil and C.L. Wilkins, "Fourier Transform Mass Spectrometry: Recent Instrument Developments and Applications", *Mass Spectrom Rev.* 5, 107-166 (1986).

16. R.S. Brown and C.L. Wilkins, "Laser Desorption Fourier Transform Mass Spectrometry of Chlorophyll A and Chlorophyll B", *J. Am. Chem. Soc.* 108, 2447-2448 (1986).

17. I.C. Bowater, R.S. Brown, J.R. Cooper and C.L. Wilkins, "Maximum Absorbance Algorithm for Reconstruction of Gas Chromatograms from Gas Chromatography/Infrared Spectrometry Data", *Anal. Chem.* 58, 2195-2199 (1986).

18. E.S. Schmidt, T.C. Bruice, R.S. Brown and C.L. Wilkins, "Oxygen Transfer from an Ozonide to Tetraphenyl-Porphyrin Chromium (III) Chloride", *Inorg. Chem.* 25, 4799-4800 (1986).

19. R.S. Brown and C.L. Wilkins, "Laser Desorption Fourier Transform Mass Spectrometry of Synthetic Porphyrins", *Anal. Chem.* 58, 3196-3199 (1986).

20. R.S. Brown and C.L. Wilkins, "Current Status of High Mass Analysis by Fourier Transform Mass Spectrometry", *Mass Spectrometry in the Analysis of Large Molecules*, Edited by C.J. McNeal, John Wiley and Sons, Ltd. (1986).

21. R.S. Brown and C.L. Wilkins, "Analytical Applications of Laser Desorption Fourier Transform Mass Spectrometry", *ACS Symposium Series* 359, Chapter 8 (1987).

PUBLICATIONS (Continued)

22. R.S. Brown and C.L. Wilkins, "A Cryogenically Cooled Interface for Gas Chromatography/Fourier Transform Infrared Spectrometry", *Anal. Chem.* 60, 1483-1488 (1988).

23. R.S. Brown and C.L. Wilkins, "Laser Mass Spectrometry: Application to Polymer Analysis", (Chapter 1 in *Applications of Lasers in Polymer Science and Technology*, Vol. 4, 1990, CRC Press, Boca Raton, FL).

24. R.S. Brown and N.L. Gilfrich, "Fourier Transform Infrared Spectrometry Coupled with Cryogenic Trapping for the Study of Laser Desorbed Neutrals", *Appl. Spectrosc.* 44, (8), 1399-1404 (1990).

25. R.S. Brown and J.J. Lennon, "Factors Affecting Sensitivity in Lightpipe Gas Chromatography Fourier Transform Infrared Spectrometry Interfaces", *Appl. Spectrosc.* 45 (4), 666-672 (1991).

26. R.S. Brown and N.L. Gilfrich, "Design and Performance of a Matrix Assisted Laser Desorption Time-of Flight Mass Spectrometer Utilizing a Pulsed Nitrogen Laser", *Anal. Chim. Acta.* 248, 541-552 (1991).

27. R.S. Brown and N.L. Gilfrich, "Optimizing Signal and Mass Resolution for Matrix Assisted Laser Desorption Utilizing a Linear Time-of-flight Mass Spectrometer" *Rapid Comm. in Mass Spectrom.* 6(11), 697 (1992).

28. R.S. Brown and N.L. Gilfrich, "Ion Detection limitations to Mass Resolution in Matrix Assisted Laser Desorption Time-of-flight Mass Spectrometry" *Rapid Comm. in Mass Spectrom.* 6(11), 690 (1992).

29. R.S. Brown and N.L. Gilfrich, "Maximum Likelihood Restoration Data Processing Techniques Applied to Matrix Assisted Laser Desorption Mass Spectra",*Appl. Spectrosc.* 47(1), 103 (1993).

30. R.S. Brown and J.J. Lennon, "Mass Resolution Improvement by Incorporation of Pulsed Ion Extraction in a Linear Time-of-Flight Mass Spectrometer", *Anal. Chem.*, 67(13), 1998 (1995).

31. B.L. Carr and R.S. Brown, "Matrix Isolation/Fourier Transform Infrared Spectrometry of Laser-Desorbed Species", *Appl. Spectrosc.*, 49(7), 955 (1995).

32. R.S. Brown and J.J. Lennon, "Sequence Specific Fragmentation of Matrix Assisted Laser Desorbed Protein/Peptide Ions", *Anal. Chem.*, 67(21), 3990 (1995).

33. R.S. Brown, B.L. Carr and J.J. Lennon, "Factors Influencing the Observed Fast Fragmentation of Peptides in Matrix Assisted Laser Desorption", *JASMS*, 7, 225 (1996).

34. R.S. Brown, J. Feng and D.C. Reiber, "Further Studies of In-Source Fragmentation of Peptides in Matrix-Assisted Laser Desorption/Ionization", *Int. J. Mass Spectrom. Ion*

PUBLICATIONS (Continued)

Processes, 169-170, 169 (1997).

35. D.C. Reiber, T.A. Grover and R.S. Brown, "Identifying Proteins Using Matrix-Assisted Laser Desorption/Ionization In-Source Fragmentation Data Combined with Database Searching" *Anal. Chem.*, 70(4), 673 (1998).

36. D.C. Reiber, S. Weinberger, J. Kenny, J. Bailey and R.S. Brown, "Unknown Peptide Sequencing Using Matrix-Assisted Laser Desorption/Ionization and In-Source Decay" *Anal. Chem.*, 70(6), 1214 (1999).

37. E. E. Durrant and R.S. Brown, "Metastable Ion Decay of Peptides and Proteins in MALDI TOF-MS Using IR and UV Desorption", *The Proceedings of the 47thASMS Conference on Mass Spectrometry and Allied Topics*", 1058, 1999.

38. E. E. Durrant and R.S. Brown, "A Comparison of IR-MALDI and UV-MALDI In-Source Decay of Peptides and Proteins", *The Proceedings of the 47th ASMS Conference on Mass Spectrometry and Allied Topics*", 1116, 2000.

39. C.R. LaPerriere and R.S. Brown, "Use of a Second Extraction Pulse to Improve the TLF Focussing of Ions in Delayed Extraction MALDI", *The Proceedings of the 48th ASMS Conference on Mass Spectrometry and Allied Topics*", 1537, 2000.

40. C.R. LaPerriere and R.S. Brown, "Optimizing The Extraction Voltage Waveform To Improve The TLF Focussing Of Ions In Delayed Extraction MALDI" *The Proceedings of the 49th ASMS Conference on Mass Spectrometry and Allied Topics*", 2001.

SUBMITTED MANUSCRIPTS

40. J. Feng, E. E. Durrant and R.S. Brown, "Synthesis of Various Substituted Cinnamic Acids and Their Application for Matrix-Assisted Laser Desorption/Ionization of Peptides and Proteins", Submitted for publication in the *Journal of Mass Spectrometry* (revised and resubmitted).

41. J. Feng and R.S. Brown, "Factors Affecting the Extent of Multiple Protonation of Protein Analytes in Matrix-Assisted Laser Desorption/Ionization Mass Spectrometry", Submitted for publication in the *Journal of Mass Spectrometry (under revision).*

42. B. Bennett;, V. D'souza, R.S. Brown, R.C. Holz, "The Anti-Angiogenesis Agent Fumagillin does not Coordinate to the Dinuclear Active Site of the Methionyl Aminopeptidase from Escherichia coli." Submitted for publication in the *Journal of the American Chemical Society.*

MANUSCRIPTS IN PREPARATION

43. J. Feng and R.S. Brown, "Development of New Co-Matrix Systems for MALDI Mass Spectrometry", To be submitted for publication in the *Journal of the American Society for Mass Spectrometry.*

45. E. E. Durrant and R.S. Brown, "IR-MALDI Employing a Short Pulsewidth Nd:YAG Pumped OPO", To be submitted for publication in *Analytical Chemistry.*

MANUSCRIPTS PLANNED

46. E. E. Durrant and R.S. Brown, "Effect of Desorption Wavelength on Post-Source Ion Decay in IR-MALDI", To be submitted for publication in *Journal of the American Society for Mass Spectrometry.*

47. E. E. Durrant and R.S. Brown, "Comparison of In-Source Decay Fragmentation Pathways in UV-MALDI and IR-MALDI", To be submitted for publication in *Journal of the American Society for Mass Spectrometry.*

BOOK REVIEWS

1. Review of "Practical Fourier Transform Infrared Spectrometry: Industrial and Laboratory Chemical Analysis", *J. Am.. Chem.. Soc.* 112, 6454 (1990).

2. Review of "Time-of-Flight Mass Spectrometry and Its Applications", *J. Am.. Soc. Mass Spectrom..* 5, 949, (1994).

STUDENT RESEARCHERS SUPERVISED (1987 - Present)

GRADUATE STUDENTS

Nancy Lynn Gilfrich, Ph.D. - May 1992 (CSU)
Thesis Title: "X-ray Fluorescence Macroprobe Analysis of Slates and Matrix Assisted Laser Desorption of Biomolecules"

Bryan Carr, Ph.D. - December 1995 (CSU)
Thesis Title: "Fourier Transform Infrared Spectrometry/Matrix Isolation of Laser Desorbed Species"

John Lennon, Ph.D. - September 1996 (CSU)
Thesis Title: "Delayed Pulsed Ion Extraction MALDI Linear Time-of-Flight Mass Spectrometry"

Duane Reiber, Ph.D. - June 1999 (USU)
Thesis Title: "The Utility of Hydroxy Substituted Benzophenones as MALDI Matrices and Peptide/Protein Sequencing Using Delayed Extraction MALDI Time-of-flight Mass Spectrometry and In-Source Fragmentation"

GRADUATE STUDENTS (Continued)

Jinhua Feng, Ph.D. - June 1999 (USU)
Thesis Title: "Synthesis and Characterization of Substituted Cinnamic Acid Derivatives as Matrices for Matrix-Assisted Laser Desorption/Ionization Mass Spectrometry"

Edward Durrant, Ph.D. - June 2001(USU)
Thesis Title: "Comparison of Ultraviolet and Infrared Matrix-Assisted Laser Desorption Ionization Time-of-Flight Mass Spectrometry"

Craig LaPerriere	MS Candidate (Writing thesis – Expected Graduation Spring 2003)
Thesis Title:	"Dynamic Delayed Extraction For MALDI TOF-MS"

CURRENT UNDERGRADUATE RESEARCH STUDENTS

Nate Maeser	USU ChemistryUndergraduate Student (BS Expected Spring 2003)

FORMER UNDERGRADUATE RESEARCH STUDENTS

John Jones	M.S. Oregon State University (1997)
Peter Staples	Exchange student from Australia
John Lane	Employed by Eli Lilly and Co., St. Louis, MO
Todd Rhea	Employed by Spectrace, Ft. Collins, CO
Dawn Richards	Present Status Unknown
Dan Meyers	Employed by EPA, Denver, CO

PROFESSIONAL SERVICE RELATED ACTIVITIES

NATIONAL SYMPOSIA ORGANIZED

1. "Laser Desorption Ionization - Fundamentals" at the 43rd ASMS Conference on Mass Spectrometry and Allied Topics, May 24, 1995, Atlanta, GA. (Organizer and Session Chair).

2. "MALDI Design and Fundamentals" at the 45th ASMS Conference on Mass Spectrometry and Allied Topics, June 5, 1997, Palm Springs, CA. (Co-Organizer and Session Co-Chair).

3. General Chairman and Program Organizer for the 6th International Desorption Conference (Desorption 2002) held Sept. 1-5, 2002 in Estes Park, CO.

4. Program Organizer for 2002 EAS Analytical Award Symposium Honoring Prof.

Charles Wilkins. Held at EAS meeting, November, 2002, Sommerset, NJ.

OUTSIDE CONSULTING

1. Consultant to Tulane University on the purchase of a high resolution mass spectrometer (Oct. 1989 - June 1990).
2. Consultant to Hybritech, Inc. (Sept. 1991 - June 1994).
3. Consultant to DuPont (Oct. 1994 - Present).
4. Consultant to Hewlett Packard Co. (Jan. 1996 - Oct. 1997).
5. Consultant to Phillips Petroleum Co. (Aug. 1997 - 2001).
6. Consultant to PE Biosystems (June 1999 - Present).
7. Consultant to Ciphergen Biosystems (July 2002 – Present)

OUTSIDE STUDY SECTIONS AND REVIEW PANELS

1. National Science Foundation, Directorate for Education and Human Resources, Instrumentation and Laboratory Improvement Program, panel member, January 1991.
2. National Science Foundation, Directorate for Education and Human Resources, Instrumentation & Laboratory Improvement Program, panel chairman, January 1992.
3. National Science Foundation SBRI review panel member, July 1995.
4. National Science Foundation Major Research Instrumentation Program (Bio Instrumentation) review panel member (appointed March 1997 through April 1999).
5. National Institutes of Health - Ad hoc member of Metallobiochemistry Study Section - Spring 1999.
6. National Institutes of Health - Ad hoc member of Metallobiochemistry Study Section, Special Emphasis Panel (BMT SEP) - February 2000.
7. National Institutes of Health - Ad hoc member of Metallobiochemistry Study Section, Special Emphasis Panel (BMT SEP) - June 2000.
8. National Institutes of Health - Ad hoc member of Chemical Instrumentation Special Study Section - Nov. 13, 2000.

PEER REVIEWER FOR THE FOLLOWING AGENCIES

1. NSF (Various divisions including: Chemistry, Biological Instruments, and Chemical Instrumentation)
2. NIH (Outside Reviewer for Metallobiochemistry Study Section)
3. DOD (Army)
4. Environmental Protection Agency
5. DOE

PEER REVIEWER FOR FOLLOWING JOURNALS

1. Analytical Chemistry
2. Journal of the American Society for Mass Spectrometry
3. Analyst
4. Applied Spectroscopy
5. Journal of Mass Spectrometry
6. International Journal of Mass Spectrometry and Ion Processes
7. Rapid Communications in Mass Spectrometry

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PATENT APPLICATION
Attorney Docket No.: SYP-060RECN

UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Marvin L. Vestal		
Application No.:	09/755,951	Art Unit:	1743
Filed:	January 4, 2001	Examiner:	Arlen Soderquist
For:	Mass Spectrometer System and Method for Matrix-Assisted Laser Desorption Measurements		

SECOND DECLARATION OF ROBERT S. BROWN UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Sir:

I, Robert S. Brown, hereby declare as follows:

1. I am currently a tenured Professor of Chemistry, Department of Chemistry and Biochemistry, at Utah State University. I have served on the Chemistry and Biochemistry Department faculty since January of 1994. Prior to that I served as an Assistant Professor on the faculty of the Chemistry Department at Colorado State University. I hold a Ph.D. in Chemistry from the Virginia Polytechnic Institute and State University. As a research scientist, I began work in the field of mass spectrometry in 1983. In the past 20 years I have contributed to the development of the mass spectroscopy field in general and matrix assisted laser desorption/ionization (MALDI) mass spectrometers in particular. I have published numerous articles on mass spectroscopy, time-of-flight mass spectroscopy and laser desorption/ionization ion sources for use with mass spectrometers.

2. During my career, I have developed a number of time-of-flight mass spectrometers and mass spectrometry techniques. In particular, I have developed several laser desorption/ionization time-of-flight mass spectrometers and techniques for their use.

3. During my career, I have supervised and served as a thesis advisor to graduate students in doctoral programs at Utah State University and Colorado State University since at least 1987. In addition, I have taught numerous undergraduate and graduate courses in which part of the subject matter concerns mass spectrometry since at least 1987. Also, since 1983 I have regularly attended professional meetings in the field of mass spectrometry. I am therefore familiar with the spectrum of skill levels of workers in the field of mass spectrometry.

4. My experience and education, including a list of publications I have authored, are summarized in my *curriculum vitae*, a true and accurate copy of which is provided with this declaration.

5. Prior to the filing of the present patent application (U.S.S.N. 09/755,951), I was retained as a consultant to Applied Biosystems a Division of Applera Corp. and the successor to PerSeptive Biosystems (hereafter "Applied Biosystems"). I have been compensated for these services at my customary rate of $2,000.00 per day of consultation. It is my understanding that I continue to be retained as a consultant to Applied Biosystems at my customary rate for the present patent application. My compensation for these services is not contingent upon the issuance of the present patent application or outcome of this or any other action.

6. In preparing this declaration, I have reviewed the following documents:

- U.S. Patent No. 5,498,545 issued on March 12, 1996, to Vestal, and reissued as RE37,485 on December 25, 2001 to Vestal;
- A copy of U.S. Application No. 09/755,951 filed on January 4, 2001. ("the Vestal application");

- A copy of the currently pending claims in U.S. Application No. 09/755,951 as of December 5, 2002. ("the Vestal claims" or "the pending claims");
- U.S. Patent No. 5,288,644 issued on February 22, 1994 to Beavis et al. ("the Beavis patent");
- U.S. Patent No. 5,045,694 issued on September 3, 1991 to Beavis et al. ("the'694 patent");
- "An Automatic Analytical Laboratory for Mass-Spectrometric Isotopic-Dilution Analysis of Uranium and Plutonium in Fuel Solutions," Safegaurds Tech., Proc. Symp., 2, pages 165-176 (1970) by Wilhelmi et al. ("the Wilhelmi article");
- U.S. Patent No. 5,382,793 issued on January 17, 1995 to Weinberger et al. ("the Weinberger patent");
- "Automated Sample Transport System for Chromatography/ Secondary Ion Mass Spectrometry" Rev. Sci. Instrum. 60 (6), pages 1071-1074 (1989) by Duffin et al. ("the Duffin article");
- U.S. Patent No. 5,037,611 issued on August 6, 1991 to Ledford ("the Ledford patent");
- "A Direct Insertion Sample Handling System for Mass Spectrometers" Int. J. Mass Spectrom. Ion Phys., 3, pages 159-160 (1969) by Bakker and Williams ("the Bakker article");
- The Office Action mailed from the U.S. Patent and Trademark Office on January 24, 2003, for U.S. Application No. 09/755,951;
- The Office Action mailed from the U.S. Patent and Trademark Office on September 8, 2003, for U.S. Application No. 09/755,951 ("the Office Action");
- "Experiments with an Automatic mass Spectrometer in the Isotopic Analysis of Nuclear Fuels" Advances in Mass Spectrometry, 7B, pages 1052-1061 (1978) by Koch et al. ("the Koch article");
- U.S. Patent No. 4,911,815 issued on March 27, 1990 to Kamei et al.;
- "Improvements in the Application of a Tandem Van De Graff Accelerator for Ultrasensitive Mass Spectrometry" Argonne National Lab., Physics Div. ANL/PHY-81-1, pages 87-99 (1981) by Suter et al.;
- "Characterization and Improvement of Gaseous Contamination Levels in a Multi-Chamber Etch Tool" 39th Proceedings-Institute of Environmental Sciences, Vol. 1, pages 124-127 (1993); and

- The Declaration of Robert S. Brown Under 37 C.F.R. § 1.132 (the "First Declaration") filed on July 24, 2003, with U.S. Patent and Trademark Office, for U.S. Application No. 09/755,951, together with a Reply to the Office Action mailed from the U.S. Patent and Trademark Office on January 24, 2003, for U.S. Application No. 09/755,951.

7. My statements in this declaration are based upon my knowledge of the mass spectrometry field, over 20 years of experience with the field and practitioners, and review of the documents listed in paragraph 6. Against this backdrop, I make the following statements of fact and observations.

8. I have been asked to evaluate the references cited in the Office Action. I will refer to the references cited in the Office Action collectively as the cited references. I have also been asked to evaluate the Vestal application and pending claims. In my evaluation, I have been asked to consider the state of the mass spectrometry field as it existed on July 21, 1994. It is my understanding that the present application claims the benefit of July 21, 1994, as its effective filing date.

9. I have considered and been asked to evaluate to what extent, if any, the cited references disclose a system for obtaining mass data having one or more of the following features:

(1) a system having a sample support transfer mechanism adapted to:

disassociate a first sample support from a sample receiving stage, transport the first sample support from an ion source chamber through an output port to a vacuum lock chamber and to associate the first sample support with a sample support holder; and

disassociate a second sample support from the sample support holder, transport the second sample support from the vacuum lock chamber through the output port to the ion source chamber and to associate the second sample support with the sample receiving stage;

(2) the system of (1) above including a mechanism to move the sample receiving stage in an x direction and in a y direction perpendicular to the x direction, where the x direction and the y direction lie substantially in the same plane;

(3) the system of (1) or (2) above where the system is configured so the vacuum lock chamber and the ion source chamber are in fluid communication and under a vacuum controlled environment during disassociation, transportation and association of the first and second sample supports;

(4) the system of (1), (2), or (3) above where the sample support holder is disposed in the vacuum lock chamber or sample storage chamber;

(5) the system of (1), (2) or (3) above where a sample storage chamber is connected to the vacuum lock chamber; or

(6) the system of (5) above where the sample support holder is disposed in the sample storage chamber.

In evaluating whether the above systems of (1)-(6) are disclosed in the cited references, I have considered the vacuum lock chamber to be connected with the ion source chamber. I have also evaluated what was described or suggested in the cited references, both separately and together, to one of ordinary skill in the field of mass spectrometry as it existed on July 21, 1994, regarding the use of the systems above to obtain mass data. As a shorthand, I will refer to the support transfer mechanism of (1) above as the "Vestal transfer mechanism".

10. I have also considered and been asked to evaluate to what extent, if any, the cited references disclose a method for obtaining mass data having at least the following steps:

(1) moving a first sample support associated with a sample receiving stage within an ion source chamber in an x direction and in a y direction perpendicular to the x direction;

striking with a laser pulse a desired number of a plurality of samples on the first sample support within the ion source chamber to desorb and ionize sample molecules;

disassociating the first sample support from the sample receiving stage;

transporting the first sample support form the ion source chamber to a vacuum lock chamber;

associating the first sample support with a sample support holder;

disassociating a second sample support from the sample support holder;

transporting the second sample support from the vacuum lock chamber to the ion source chamber;

associating the second sample support with the sample receiving stage;

moving the second sample support associated with the sample receiving stage within the ion source chamber in an x direction, and in a y direction perpendicular to the x direction; and

striking with a laser pulse a desired number of a plurality of samples on the second sample support within the ion source chamber to desorb and ionize sample molecules; or

(2) the method for obtaining mass data including the steps of (1) above in this paragraph where the vacuum lock chamber and ion source chamber are in fluid communication and are maintained under a vacuum controlled environment during the dissociating, transporting, and associating of the first and second sample supports.

I have also evaluated what was described or suggested in the cited references, both separately and together, to one of ordinary skill in the field of mass spectrometry as it existed on July 21, 1994, regarding the use of the steps above to obtain mass data.

11. I have been asked based on my knowledge (which includes over 20 years of experience in the mass spectrometry field, and contemporaneous knowledge of both the mass spectrometry field and those of ordinary skill in this field as it existed on July 21, 1994) whether the systems for obtaining mass data as described in the Vestal application and Vestal claims 75-87, 90-91, 95 and 97, when viewed as a whole, was known to the mass spectrometry field, as it existed on July 21, 1994, or that practicing one or more of Vestal claims 75-87, 90-

91, 95 and 97, as a whole was recommended by or apparent to one of ordinary skill in the art in the mass spectrometry field as it existed on July 21, 1994.

12. I have also been asked based on my knowledge (which includes over 20 years of experience in the mass spectrometry field, and contemporaneous knowledge of both the mass spectrometry field and those of ordinary skill in this field as it existed on July 21, 1994) whether the methods for obtaining mass data as described in the Vestal application and Vestal claims 92-94 when viewed as a whole, was known to the mass spectrometry field, as it existed on July 21, 1994, or that practicing one or more of Vestal claims 92-94 as a whole was recommended by or apparent to one of ordinary skill in the art in the mass spectrometry field as it existed on July 21, 1994.

13. It is my understanding that a person of ordinary skill in the art is one who thinks along the line of conventional wisdom in the art. A person of ordinary skill in the art is not one who undertakes to innovate, whether by patient, and often expensive, systematic research or by extraordinary insights. Based on my over 20 years of experience in the mass spectrometry field, and contemporaneous knowledge of both the mass spectrometry field and practitioners of all skill levels in this field as it existed on July 21, 1994, one of ordinary skill in the field of mass spectrometry as it existed on July 21, 1994 would have possessed an education in Chemistry or Physics at a Masters degree level and been competent in the use of mass spectrometry instrumentation. I understand that one of ordinary skill in the art is a "hypothetical person" who does not necessarily exist.

14. I have again reviewed the Vestal application. In view of paragraph 13 above, I maintain and reiterate my reading and view of the Vestal application expressed in paragraphs 13, 14 and 15 of my First Declaration. It is my view that one of ordinary skill in the field of mass spectrometry, upon reading the Vestal application, would understand that the Vestal application describes systems where a sample support holder can be placed in the vacuum lock chamber even for those systems that do not have a sample storage chamber. In my view and

based on my experience with practitioners in the field, upon reading the Vestal application one of ordinary skill in the field of mass spectrometry would also understand that the Vestal application describes structures and methods that permit the vacuum lock chamber and the ion source chamber to be in fluid communication while also under a vacuum controlled environment during disassociation, transportation and association of sample supports. It is my view that one of ordinary skill in the field of mass spectrometry would understand that such systems are included in the description at column 6, line 50, to column 9, line 51, of the Vestal application. It is also my view that one of ordinary skill in the field of mass spectrometry would understand that methods for obtaining mass data using a sample support holder in the vacuum lock chamber without a sample storage chamber, and methods where the vacuum lock chamber and the ion source chamber are in fluid communication while also under a vacuum controlled environment during disassociation, transportation and association of first and second sample supports, are both described by the Vestal application.

15. I understand the Vestal application to claim and describe various systems that include a transport mechanism configured to transport sample supports to and from an ion source chamber through an output port to a vacuum lock chamber and to associate and dissociate sample supports with a sample support holder and sample receiving stage as discussed in paragraph 9 above. I understand the Vestal application to describe and claim in claims 75-87, and 95 a system that includes a mechanism to move the sample receiving stage in an x direction and in a y direction perpendicular to the x direction, where the x direction and the y direction lie substantially in the same plane. I also understand the Vestal application to describe and claim in claims 90-91 and 97 a system that includes a sample storage chamber connected to the vacuum lock chamber. I further understand the Vestal application to describe and claim in claims 95 and 97 a system that includes structures configured so that the vacuum lock chamber and the ion source chamber are in fluid communication while also under a vacuum controlled environment during disassociation, transportation and association of the first and second sample supports. In addition, I understand the Vestal application to describe the use of a sample

support holder capable of holding multiple sample supports in the vacuum lock chamber or a sample storage chamber. As a shorthand, I will refer to the various systems laid out in Vestal claims 75-87, 90-91, 95, and 97 collectively as the "Vestal systems."

16. I understand the Vestal application to claim methods for obtaining mass data. I understand from the Vestal application that the methods laid out in claims 92-94 involve using at least the steps of (1) in paragraph 10. I further understand from the Vestal application that the method laid out in claim 93 involves having the vacuum lock chamber and ion source chamber in fluid communication while also under a vacuum controlled environment during the dissociating, transporting, and associating of the first and second sample supports. As a shorthand term, I will refer to the methods laid out in Vestal claims 92-94 collectively as the "Vestal methods."

17. I understand the Beavis patent to describe a system where a sample disk is attached directly to the shaft of a stepper motor and the sample disk is then somehow loaded into the ion source through a vacuum lock. However, I can find no description in the Beavis patent that describes how one could either attach or detach the sample disk of Beavis to the stepper motor under a vacuum controlled environment. It is my view that Beavis indicates that attachment and detachment do not occur under a vacuum controlled environment at column 4, lines 65-67, when he instructs that, "any gas introduced in this procedure [the insertion of a disk into the ion source] must be removed prior to measuring the mass spectrum," and at column 5, lines 25-29, where Beavis indicates that pumpdown is required after inserting a new sample disk, "less than five minutes of each two hour period is required for loading and pumpdown." Based on my experience, the Beavis patent provides no description or suggestion to one of ordinary skill in the field of mass spectrometry of how to load sample disks while under a vacuum controlled environment onto the stepper motor or onto any other device that can move the sample disk. Based on my experience, the Beavis patent also does not provide any guidance to one of

ordinary skill in the field on how to modify his system to load sample disks under a vacuum controlled environment.

18. I can find no description in the Beavis patent that describes the use of a sample support holder in either a vacuum lock chamber connected with the ion source chamber or a sample storage chamber connected to the vacuum lock chamber. In addition, I can find no description in the Beavis patent that describes a transport mechanism configured to transport sample supports to and from an ion source chamber through an output port to a vacuum lock chamber and to associate and dissociate sample supports with a sample support holder and sample receiving stage as discussed in paragraph 9 above. Based on my experience, the Beavis patent also does not provide any guidance to one of ordinary skill in the field on how to modify his system to include a sample support holder or a transport mechanism as discussed in paragraph 9 above.

19. I have also reviewed the '694 patent which I understand to be the patent which issued from U.S. Patent Application Serial No. 07/413,321 referenced at column 5, lines 5-10 in the Beavis patent. I have been asked to review the '694 patent to place in context the phrase "even if the samples were manually loaded, as disclosed in [sic] copending U.S. Pat. application Ser. No. 07/413,321" appearing at column 5, lines 5-10, in the Beavis patent. The '694 patent does not describe any structure for rotation or x-y translation of the sample probe once inside the ion source. The '694 patent does refer to sample loading, in the same fashion it is referred to in the Beavis patent, at column 6, lines 29-31 which reads, "With a typical sample loading of 0.1-20 p mol of analyte on the probe tip (3 mm^2) good signals were observed." Based on my experience and the lack of any description in the '694 patent of specific probe movement once inside the ion source, and the use of the term sample loading to refer to spotting of the sample on a probe tip, I understand and one of ordinary skill in the field of mass spectrometry would understand the text in the Beavis patent on manual and automatic sample loading to be referring to the spotting of samples onto the sample disk and not the loading of a sample disk onto a stepper

motor. In addition, I understand and one of ordinary skill in the field of mass spectrometry would understand the text at column 4, lines 4-9, in the '694 patent ("The probe **10** is manually inserted and may be manually removed from the round bore **12** of the metal wall **13** of the spectrometer"), to not be the part of the '694 patent the Beavis patent is referring to at column 5, lines 5-10 because this part of the '694 patent only concerns the probe and the Beavis patent makes clear that sample loading refers to the loading of sample onto the sample disk.

20. I have again reviewed the Beavis patent with respect to what one of ordinary skill in the field of mass spectrometry would understand the text in the Beavis patent to suggest. Particularly, I have again reviewed the paragraph in the Beavis bridging columns 4 and 5, and lines 5-10 at column 5 in the Beavis patent. In my view, one of ordinary skill in the field of mass spectrometry would not understand the Beavis patent to suggest automation of sample disk insertion into or transport of the sample disk within a mass spectrometer, for many reasons. First the paragraph bridging columns 4-5 refers to a singular disk, not multiple disks. The sentences at lines 5-10 refer to sample loading, making no mention of sample disk insertion. Based on my experience, one could not reasonably read into lines 5-10 a reference to sample disk insertion and one of ordinary skill in the field would not read these lines as referring to sample disk insertion. Based on my experience, one of ordinary skill in the field would read the reference in lines 5-10 to sample loading to refer to the meaning and context they are given throughout the Beavis patent. I and one of ordinary skill in the field would understand that the Beavis patent clearly shows that sample loading is the loading, shown to be spotting, of sample onto a sample disk. I and one of ordinary skill in the field would understand that the Beavis patent's Figure 1 clearly illustrates one such sample loading approach which he calls, "a suitable automated DNA sample preparation and loading technique" and that this is what the Beavis patent refers to when in column 5, lines 14-17, he claims "The technique of the present invention does not...require the full time attention of a dedicated, trained operator to prepare and load the samples." I and one of ordinary skill in the field would understand that the time savings the Beavis patent is discussing in column 5, lines 5-10, and the bridging paragraph of

columns 4-5, are those given by using mass spectrometry instead of gel electrophoresis to analyze a sample and (with Figure 1 and the Beavis patent's claim in column 5, lines 14-17, that the full time attention of a dedicated, trained operator to prepare and load the samples is not required) automated preparation of samples and automated loading onto a sample disk. Thus, I do not understand, and in my view one of ordinary skill in the field of mass spectrometry would not understand the Beavis patent to suggest automation of sample disk insertion into a mass spectrometer or suggest the automation of the transport of the sample disk within a mass spectrometer.

21. I understand the Wilhelmi article to be concerned with mass spectrometric measurements of uranium and plutonium in nuclear fuel samples placed as solutions onto evaporator filaments (which I subsequently refer to as sample filaments) and dried prior to mass spectrometry analysis. Based on an examination of Figure 3 and its description, Wilhelmi appears to illustrate a system that uses several mechanisms to move a cassette containing beads of nuclear material where each bead is deposited on heating filament. The Wilhelmi system appears to use a mechanism to place the cassette into a preheating chamber and a mechanism is presumably used to move the heated cassette to a lock chamber. A separate pushrod mechanism is used to push a sample filament (referred to as a "bead" in the article) into the ion source where it is vaporized by heating the filament, which appears to also be referred to as an evaporation filament. The vapor that results is then ionized by electrons emitted by the ionization filament in the ion source (electron impact ionization).

22. However, it is my view that the Wilhelmi article does not describe or suggest that the sample filament (or bead) is ever detached from the end of the pushrod (also referred to as a "pinch rod" in the text) during mass spectrometric analysis. It is my view that the sample filament probably does not leave the end of the pushrod based on several parts of the text description. First, the Wilhelmi article does not mention any separate stage to receive a sample filament. Second, the Wilhelmi article states at page 172 that "as soon as the bead is introduced

into the ion source the measurement starts" indicating in my view that the pushrod does not detach from the bead (sample filament) during this step. Third, because there is only one sample filament, sample bead, introduced at a time into the ion source and the sample is vaporized by heating a sample filament, there appears to be no reason to associate the sample filament with a separate stage. Based on my experience, the Wilhelmi article provides no description or suggestion to one of ordinary skill in the field of mass spectrometry to associate or disassociate a sample support with a receiving stage, or any guidance to one of ordinary skill in the field on how to modify his mechanism to either associate or disassociate a sample support with a receiving stage.

23. Making use of the drawing item numbers in the Weinberger patent, I understand the Weinberger patent to describe a system where a shaft (154) is used to pick up a probe tip (30) from a sample ring (152), the probe tip is then pushed into an ion optics region (32) but the probe remains attached to the shaft during mass spectrometric analysis because it is used to rotate the probe tip which contains the sample for analysis. The shaft (154) has o-ring seals (shown in Figure 6), one of which vacuum isolates the ion optics region (32) from the sample chamber (28) containing the sample ring (152) once the ball valve lock (172) is opened and a probe tip has been fully inserted. This o-ring seal prevents fluid communication between the sample chamber (28) and ion optics region (32) by apparently sealing against the ion optic entrance channel (170) when the ball valve lock (172) is opened and the probe tip is fully inserted. The Weinberger patent's structure of a shaft in a channel also prevents x-y translation of the probe during mass spectrometric analysis.

24. It is my view that the Weinberger patent does not describe or suggest a structure that enables a sample support to be dissociated from a transport mechanism and associated with a receiving stage. It is also my view that the structures described and suggested by the Weinberger patent are incompatible with the use of a receiving stage that provides x-y translation because they technically cannot be made to work with such a receiving stage because

modification of the shaft of the Weinberger patent for combination with Beavis to execute x-y translation, would render the mechanism of the Weinberger patent inoperable for its intended purpose. More specifically, the mechanism of the Weinberger patent includes the shaft (154) with o-ring seals and an entrance channel arrangement which is meant to operate so the o-rings on the shaft seal against the ion optic entrance channel (170) when the probe tip is fully inserted and yet allow the shaft to rotate the probe tip while vacuum isolating the ion optics region (32) from the sample chamber (28). Using the technical teachings of the Weinberger patent, modification of the Weinberger patent shaft channel assembly so the shaft could execute x-y translation would disrupt the seal provide by the shaft o-ring which isolates the ion optics region, and this would render the Weinberger patent mechanism inoperable for its intended purpose. Based on my experience, the Weinberger patent does not provide any guidance to one of ordinary skill in the field on how to modify his mechanism to either: (a) associate or disassociate a sample support with a receiving stage; (b) associate or disassociate a sample support with a receiving stage that provides x-y translation; or (c) permit a vacuum lock chamber and an ion source chamber to be in continuous fluid communication while also under a vacuum controlled environment during disassociation, transportation and association of sample supports; as any of these are set forth in Vestal claims 75-87, 90-94, 95, and 97 or in a manner equivalent to those described in (1)-(6) in paragraph 9 above.

25. I understand the Duffin article to describe a piezoelectric actuated x-y translation stage. However, the Duffin article does not describe or suggest the use of any mechanism that can either transport a sample support to and from an ion source chamber to a vacuum lock chamber or associate and dissociate sample supports with either a sample support holder or sample receiving stage other than via a manual procedure which requires venting to atmosphere the entire instrument. In my view, the Duffin article also does not provide any suggestion or description that would have provided guidance to the ordinary practitioner in the field of mass spectrometry as of July 21, 1994, on how to make or use a mechanism that could transport sample supports to and from an ion source chamber through an output port to a vacuum lock

chamber and to associate and dissociate sample supports with a sample support holder and sample receiving stage in a manner equivalent to those described in (1)-(6) in paragraph 9 above.

26. It is my understanding that the Office Action makes reference to the Ledford patent for its use of indicia to provide indexing and sample information. In my view the Ledford patent however does not describe or suggest a mechanism that could transport sample supports to and from an ion source chamber through an output port to a vacuum lock chamber and to associate and dissociate sample supports with a sample support holder and sample receiving stage in a manner equivalent to those described in (1)-(6) in paragraph 9 above.

27. I understand the Bakker article to illustrate a system with a swing butterfly valve but the Bakker article does not describe or suggest the use of any mechanism that can either transport a sample support to and from an ion source chamber to a vacuum lock chamber and associate and dissociate sample supports with a either a sample support holder or sample receiving stage. While swing butterfly valves and other vacuum isolation methods such as gate valves and ball valves would have been known to practitioners of ordinary skill in the field of mass spectrometry, the Bakker article also does not provide any suggestion or description that would have provided guidance to the ordinary practitioner in the field of mass spectrometry as of July 21, 1994, on how to make or use a mechanism that could transport sample supports to and from an ion source chamber through an output port to a vacuum lock chamber and to associate and dissociate sample supports with a sample support holder and sample receiving stage in a manner equivalent to those described in (1)-(6) in paragraph 9 above.

28. Based on my experience, there is no equivalent operator hands-on activity to a mechanism equivalent to those described in (3)-(6) in paragraph 9; or in (2) in paragraph 10 above because a human cannot associate, transport or disassociate a sample support with a receiving stage as described in (3)-(6) in paragraph 9 or in (2) in paragraph 10 while the vacuum lock chamber and the ion source chamber are in continuous fluid communication and under a

vacuum controlled environment during disassociation, transportation and association of the sample supports without exposing the operator to the detrimental effects of vacuum.

29. It is my view that while various versions of sample supports, sample holders, sample receiving stages, and mechanisms to hold and move sample supports were known to the mass spectrometry field, as of July 21, 1994, the steps necessary to modify such existing components and produce an instrument in keeping with one or more of the Vestal systems, were not known, and would not have been apparent to one of ordinary skill in the mass spectrometry field as of July 21, 1994, without the disclosure provided by the Vestal application. It is my view that the likelihood that one of ordinary skill in the field of mass spectrometry as of July 21, 1994, would have been able to modify and combine the cited references to produce one or more of the Vestal systems was remote. Thus, it is my view (based on my experience, which includes over 20 years of experience in the mass spectrometry field, and contemporaneous knowledge of both the mass spectrometry field and those of ordinary skill in this field as it existed on July 21, 1994), that one of ordinary skill in the field of mass spectrometry as of July 21, 1994, would not have had a reasonable expectation of successfully combining the cited references to produce one or more of the Vestal systems. Based on my experience, any expectation of success by one of ordinary skill in the field would have been unreasonable because it would have required extensive experimentation to determine how to modify and then modify and combine existing components to produce a system in keeping with one or more of the Vestal systems. First, absent the Vestal application, the cited references and to my knowledge the mass spectrometry field as of July 21, 1994, provided no working examples of a transfer mechanism such as the Vestal transfer mechanism. Second, absent the Vestal application, the cited references and to my knowledge the mass spectrometry field as of July 21, 1994, provided no guidance on how such existing components could be modified and combined to produce one or more of the Vestal systems.

30. Based on my experience it is my view that, absent the Vestal application, the cited references and to my knowledge the mass spectrometry field as of July 21, 1994, provided no working examples of a method for obtaining mass data in a manner equivalent to those of one or more of the Vestal methods. Based on my experience it is also my view that, absent the Vestal application, the cited references and to my knowledge the mass spectrometry field as of July 21, 1994, provided no description of an instrument or guidance on how to combine existing structures to produce a working instrument that could be used to obtain mass data in a manner equivalent to that of one or more of the Vestal methods. Thus, it is my view (based on my experience, which includes over 20 years of experience in the mass spectrometry field, and contemporaneous knowledge of both the mass spectrometry field and those of ordinary skill in this field as it existed on July 21, 1994), that one of ordinary skill in the field of mass spectrometry as of July 21, 1994, would not have had a reasonable expectation of successfully combining the cited references to practice one or more of the Vestal methods.

31. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the present application or any patent issued in reliance thereon.

Date: March 5, 2004

Robert S. Brown

Robert S. Brown, Ph.D.

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UTAH STATE UNIVERSITY

Curriculum Vitae

DEPARTMENT OF CHEMISTRY AND BIOCHEMISTRY

NAME Robert S. Brown

DATE AND PLACE OF BIRTH June 22, 1956 Medford, Massachusetts

EDUCATION

Ph.D. Analytical Chemistry, Virginia Polytechnic Institute and State University, 1983
B.S. Chemistry, University of Massachusetts at Lowell, 1978

AREAS OF SPECIAL INTEREST

Study of fundamental and applied aspects of mass spectrometry (particularly TOF-MS and FT-MS) of large molecules. Application of mass spectrometry to various chemical problems, with particular emphasis on biochemically relevant systems. Development of laser based ionization methods for mass spectrometry and their application to non-volatile sample characterization. Study of the fundamental processes involved in the matrix assisted laser desorption/ionization (MALDI) process. Synthesis of new MALDI matrix materials. New instrumental designs for TOF-MS. Ion detection processes of large m/z ions. Polymer and biopolymer structural characterization utilizing mass spectrometry.

PROFESSIONAL EXPERIENCE

Associate Professor, Utah State University, 6/98 - Present
Assistant Professor, Utah State University, 1/94 - 6/98
Assistant Professor, Colorado State University, 8/87 - 12/93
Postdoctoral Research Associate, University of Calif., Riverside 8/83 - 6/87

HONORS

Graduation cum laude, University of Lowell, 1978
Research Fellowship, Virginia Polytechnic Institute and State University, 1978-1980
Associate Member, Sigma XI

PROFESSIONAL SOCIETY AFFILIATIONS

American Chemical Society
American Society for Mass Spectrometry
Society for Applied Spectroscopy
Protein Society

UNIVERSITY AND DEPARTMENTAL COMMITTEE ASSIGNMENTS

Graduate Admissions Committee	January 1994 - August 1996
Curriculum Committee	January 1994 - May 1997
Organic Search Committee (Chairman)	June 1995 - January 1996
Building & Space Committee	August 1996 - June 1999
Building & Space Committee (Chairman)	May 1998 - June 1999
Visiting Speakers Committee	May 1997 - June 1998
Graduate Studies Committee	May 1997 - July2001
Graduate Studies Committee (Chairman)	May 1999 - July 2001
P & T Committee - Prof. Lisa Berreau	January 1998 - Present
Advisory & Evaluation Committee	
Dr. Zhihua Shen (Instructor)	September 1999 - June 2001
Departmental Library Committee	May 1999 - 2000
Shimadzu Analytical Laboratory Director	March 2000 - Present
College of Science Dean Search Committee	April 2000 - June 2001
Advisory Committee	June 2000 - Present
Advisory Committee (Chairman)	June 2000 - June 2001
Analytical Search Committee (Chairman)	July 2000 – May 2002
Lab Manager Search Committee	July 2000 - Spring 2001
General Chemistry Steering Committee	July 2000 - Present
P & T Committee - Prof. Tom Chang	January 2000 – Present
P & T Committee - Prof. Phil Silva	September 2002 - Present

TEACHING ASSIGNMENTS (Credits)

Chemistry 761 - Analytical Separations (3)	Spring 1994
Chemistry 780 - Physical-Analytical Seminar (1)	Spring 1994
Chemistry 123 - Principles of Chemistry (3)	Fall 1994
Chemistry 160 - Quantitative Analysis I (2)	Fall 1994
Chemistry 662 - Analytical Chemistry (3)	Spring 1995
Chemistry 160 - Quantitative Analysis I (2)	Spring 1995
Chemistry 780 - Physical-Analytical Seminar (1)	Fall 1995
Chemistry 761 - Analytical Separations (3)	Winter 1996
Chemistry 780 - Physical-Analytical Seminar (1)	Winter 1996
Chemistry 160 - Quantitative Analysis I (2)	Spring 1996
Chemistry 764 - Special Topics in Analytical Chemistry (1)	Spring 1996
Chemistry 360 - Quantitative Analysis II (3)	Fall 1996
Chemistry 361 - Quantitative Analysis Lab (2)	Fall 1996
Chemistry 780 - Physical-Analytical Seminar (1)	Winter 1997
Chemistry 662 - Analytical Chemistry (3)	Spring 1997
Chemistry 764 - Special Topics in Analytical Chemistry (1.5)	Spring 1997
Chemistry 780 - Physical-Analytical Seminar (1)	Fall 1997
Chemistry 121 - Principles of Chemistry (5)	Winter 1998
Chemistry 122 - Principles of Chemistry (4)	Spring 1998
Chemistry 7610 - Chemical Separations (3)	Fall 1998
Chemistry 4990 - Undergraduate Seminar (1)	Fall 1998
Chemistry 7600 - Analytical Spectroscopy (3)	Spring 1999
Chemistry 4990 - Undergraduate Seminar (1)	Spring 1999

Chemistry 4990 - Undergraduate Seminar (1)	Fall 1999
Chemistry 1210 - Principles of Chemistry (4)	Spring 2000
Chemistry 4990 - Undergraduate Seminar (1)	Spring 2000
Chemistry 4990 - Undergraduate Seminar (1)	Fall 2000
Chemistry 7610 - Chemical Separations (3)	Fall 2000
Chemistry 5640 - Instrumental Analysis (3)	Spring 2001
Chemistry 5650 - Instrumental Analysis Lab (2)	Spring 2001
Chemistry 4990 - Undergraduate Seminar (1)	Spring 2001
Chemistry 3600 - Quantitative Chemical Analysis (3)	Fall 2001
Chemistry 3610 - Quantitative Chemical Analysis Lab (1)	Fall 2001
Chemistry 5640 - Instrumental Analysis (3)	Spring 2002
Chemistry 5650 - Instrumental Analysis Lab (2)	Spring 2002
Chemistry 7610 - Chemical Separations (3)	Fall 2002
Chemistry 5640 - Instrumental Analysis (3)	Spring 2003
Chemistry 5650 - Instrumental Analysis Lab (2)	Spring 2003

PROFESSIONAL MEETINGS ATTENDED

Organization	Date	Location
Society of Western Analytical Professors Meeting	Jan. 1988	Pomona, CA
Pittsburgh Conference	Feb. 1988	New Orleans, LA
American Society for Mass Spectrometry Meeting	June 1988	San Francisco, CA
Pittsburgh Conference	March 1989	Atlanta, GA
American Society for Mass Spectrometry Meeting	June 1989	Miami, FL
American Society for Mass Spectrometry Meeting	June 1990	Tucson, AZ
MUACC Meeting	Oct. 1990	Minneapolis, MN
Pittsburgh Conference	March 1991	Chicago, IL
American Society for Mass Spectrometry Meeting	June 1991	Nashville, TN
Rocky Mountain Conference on Analytical Chemistry Meeting	July 1991	Denver, CO
Federation on Analytical Chemistry and Spectroscopy Society Meeting	Oct. 1991	Anaheim, CA
4th Sanibel Conference on Mass Spectrometry	Jan. 1992	Sanibel Island., FL
Pittsburgh Conference	March 1992	New Orleans, LA

PROFESSIONAL MEETINGS ATTENDED (Continued)

American Society for Mass Spectrometry Meeting Desorption'92	June 1992 Sept. 1992	Washington, DC Burg Waldeck, Germany
Organization	Date	Location
Pittsburgh Conference	March 1993	Atlanta, GA
American Society for Mass Spectrometry Meeting	June 1993	San Francisco,
Rocky Mountain Conference on Analytical Chemistry Meeting	August 1993	Denver, CO
Desorption '94	March 1994	Sun River Lodge, OR
1994 Pittsburgh Conference	Feb 27 - Mar 4, 1994	Chicago, IL
42nd American Society for Mass Spectrometry Conference on Mass Spectrometry and Allied Topics	May 29- June3, 1994	Chicago, IL
36th Rocky Mountain Conference on Analytical Chemistry Mass Spectrometry Symposium	Aug 1994	Denver, CO
1995 Pittsburgh Conference	March 6-9,	New Orleans,
43rd American Society for Mass Spectrometry Conference on Mass Spectrometry & Allied Topics	May 1995	Atlanta, GA
37th Rocky Mountain Conference on Analytical Chemistry Mass Spectrometry Symposium	Aug 1995	Denver, CO
1996 Pittsburgh Conference	March 3-8, 1996	Chicago, IL
44th American Society for Mass Spectrometry Conference on Mass Spectrometry and Allied Topics	May 12-16 1996	Portland, OR
38th Rocky Mountain Conference on Analytical Chemistry Mass Spectrometry Symposium	Aug. 1996	Denver, CO
10th Symposium of the Protein Society	Aug. 3-7 1996	San Jose, CA
Desorption '96	Sept. 18-21 1996	Ronne, Denmark

PROFESSIONAL MEETINGS ATTENDED (Continued)

Organization	Date	Location
Eastern Analytical Symposium	Nov. 18-21, 1996	Sommerset, NJ
1997 Pittsburgh Conference	March 16-21, 1997	Atlanta, GA
45th American Society for Mass Spectrometry Conference on Mass Spectrom. & Allied Topics	June 1-5, 1997	Palm Springs, CA
39th Rocky Mountain Conference on Analytical Chemistry Mass Spectrometry Symposium	Aug. 1997	Denver, CO
1998 Pittsburgh Conference	March 1-6, 1998	New Orleans, LA
46th American Society for Mass Spectrometry Conference on Mass Spectrom. & Allied Topics	May 31- June 4, 1998	Orlando, FL
Desorption '98	Sept. 21-26, 1998	Angra dos Reis, Brazil
HPCE Conference	January 24 26, 1999	Palm Springs, CA
1999 Pittsburgh Conference	March 1-6, 1999	Orlando, FL
47th American Society for Mass Spectrometry Conference on Mass Spectrometry & Allied Topics	June 13-18, 1999	Dallas, TX
2000 Pittsburgh Conference	March 1-6, 2000	New Orleans, LA
48th American Society for Mass Spectrometry Conference on Mass Spectrometry and Allied Topics	June 11-15, 2000	Long Beach, CA
Desorption 2000	Sept. 3-8, 2000	St. Malo, France
2001 Pittsburgh Conference	March 4-9, 2001	New Orleans, LA
49th American Society for Mass Spectrometry Conference on Mass Spectrometry and Allied Topics	May 27-31, 2001	Chicago, Il

PROFESSIONAL MEETINGS ATTENDED (Continued)

Organization	Date	Location
2002 Pittsburgh Conference	March 17-22, 2002	New Orleans, LA
50th American Society for Mass Spectrometry Conference on Mass Spectrometry and Allied Topics	June 2-6, 2002	Orlando, FL
Desorption 2002	Sept. 1-5, 2002	Estes Park, CO
Eastern Analytical Symposium	Nov. 18-21 2002	Somerset, NJ

CONFERENCE PRESENTATIONS

Title	Date	Location
"Alternative Approaches to GC/FT-IR/MS"	Feb. 1988	Pittsburgh Conference
"Mass and Infrared Spectrometry Studies of the Laser Desorption Process"	Oct. 1990	Midwest Universities Analytical Chemistry University of Minnesota
"Comparison of Theoretical and Experimental Peakshapes in Matrix Assisted Laser Desorption Mass Spectrometry"	June 1991	ASMS Meeting Nashville, TN
"Improving Ion Transfer and Detection in Matrix Assisted Laser Desorption of High Mass Biomolecules"	Oct. 1991	FACCS Meeting Anaheim, CA
"Cryogenic Trapping of Laser Desorbed Species Coupled with Fourier Transform Infrared Spectrometry"	Oct. 1991	FACCS Meeting Anaheim, CA
"Identification of Matrix Adduct Ion Species in Matrix Assisted Laser Desorption Mass Spectrometry"	Jan. 1992	4th Sanibel Conference on Mass Spectrometry Sanibel Island, FL
"Maximum Likelihood Data Processing Techniques for Improved Mass Resolution in Matrix-Assisted Laser Desorption"	Mar. 1992	Pittsburgh Conference New Orleans, LA
"Adduct Ion formation Pathways in Matrix Assisted Laser Desorption Mass Spectrometry"	June 1992	ASMS Meeting Washington, D.C.

CONFERENCE PRESENTATIONS (Continued)

Title	Date	Location
"Aspects of Large Ion Detection in Matrix Assisted Laser Desorption Mass Spectrometry"	June 1992	ASMS Meeting Washington, D.C.
"Evaluation of an Electrostatic Analyzer Based Time-Of-Flight Mass Spectrometer for Matrix Assisted Laser Desorption"	Sept. 1992	Desorption '92 Burg Waldeck, Germany
"Kinetic Energy Measurements of Matrix Assisted Laser Desorption Generated Ions With an Electrostatic Analyzer Based Time-of-flight Mass Spectrometer"	June 1993	American Society for Mass Spectrometry and Allied Topics Conference San Francisco, CA
"A Postacceleration Detector for Time-of-flight Mass Spectrometry Utilizing Ion to Photon Conversion"	June 1993	American Society for Mass Spectrometry and Allied Topics Conference San Francisco, CA
"Pulsed Ion Extraction at High Accelerating Fields in a MALDI Time-of Flight Mass Spectrometer"	Mar. 1994	Desorption '94 Sun River Lodge, OR
"Pulsed Ion Extraction Combined with High Accelerating Potentials for Matrix-Assisted Laser Desorption Time-of-Flight Mass Spectrometry"	June 1994	42nd American Society for Mass Spectrometry Conf. on Mass Spectrometry and Allied Topics Chicago, IL
"A Comparison of Various Alpha Substituted Cinnamic Acids as Matrices for Matrix-Assisted Laser Desorption"	June 1994	42nd American Society for Mass Spectrometry Conf. on Mass Spectrometry and Allied Topics, Chicago, IL
"Matrix-Assisted Laser Desorption: How Soft an Ionization Process?"	Mar. 1995	1995 Pittsburgh Conference New Orleans, LA
"Hydroxy Benzophenones: A New Class of MALDI Matrices for Proteins/Peptides"	May 1995	43rd American Society for Mass Spectrometry Conf. on Mass Spectrometry and Allied Topics, Atlanta, GA
"Fast Metastable Ion Fragmentation in MALDI"	May 1995	43rd American Society for Mass Spectrometry Conf. on Mass Spectrometry and Allied Topics, Atlanta, GA

CONFERENCE PRESENTATIONS (Continued)

Title	Date	Location
"Matrix Isolation/FT-IR Spectrometry of Laser Desorbed Neutrals"	June 1995	Regional ACS Meeting Park City, UT
"Metastable Ion Decay in Matrix-Assisted Laser/Ionization"	June 1995	Regional ACS Meeting Park City, UT
"Utilization of MALDI In-Source Decay Ions for Peptide/Protein Sequencing"	Mar. 1996	Pittsburgh Conference Chicago, IL
"Early Time Frame Metastable Ion Decay in MALDI"	May 1996	44th ASMS Conference Portland, OR
"Examination Of The Use Of MALDI In-Source Decay For Sequencing Peptides"	May 1996	44th ASMS Conference Portland, OR
"Characteristics Of Several New Alpha Substituted Cinnamic Acids As MALDI Matrices"	May 1996	44th ASMS Conference Portland, OR
"High Mass Resolution MALDI TOF Mass Spectrometry"	Aug. 1996	38th Rocky Mountain Conf. on Analytical Chemistry, Denver, CO
"Utilization of MALDI Fast Metastable Ion Decay Ions for Peptide/Protein Sequencing"	Aug. 1996	10th Protein Society Symposium San Jose, CA
"Factors Influencing Mass Resolution in Delayed Extraction TOF-MS"	Sept. 1996	Desorption '96 Ronne, Denmark
"New Strategies For Protein Sequencing Using MALDI In-Source Decay"	Mar. 1997	Pittsburgh Conference Atlanta, GA
"Synthesis and Utility of Additional Substituted Cinnamic Acid Derivative as MALDI Matrices"	June 1997	45th ASMS Conference Palm Springs, CA
"A New Instrument Design For MALDI Time-of-Flight Mass Spectrometry"	June 1997	45th ASMS Conference Palm Springs, CA
"Protein Sequencing Strategies Based Upon Enzymatic Cleavage and MALDI In-Source Decay"	June 1997	45th ASMS Conference Palm Springs, CA
"IR-MALDI Employing a Short Pulsewidth Nd:YAG Pumped OPO"	March 1998	1998 Pittsburgh Conf. New Orleans, LA

CONFERENCE PRESENTATIONS (Continued)

Title	Date	Location
"Cinnamic Acid Substitution Effects on MALDI Time-of-Flight Mass Spectrometry Performance"	March 1998	1998 Pittsburgh Conf. New Orleans, LA
"Development of New Co-Matrix Systems for MALDI Mass Spectrometry"	June 1998	46th ASMS Conf. Orlando, FL
"Protein Identification Utilizing In-Source Decay MALDI Data Combined With Database Searching"	June 1998	46th ASMS Conf. Orlando, FL
"IR-MALDI Employing a Short Pulsewidth Nd:YAG Pumped OPO"	June 1998	46th ASMS Conf. Orlando, FL
"Metastable Ion Decay of Peptides and Proteins in MALDI TOF-MS Using IR and UV Desorption"	June 1999	47th ASMS Conf. Dallas, TX
"Metastable Ion Decay of Peptides and Proteins in MALDI TOF-MS Using IR and UV Desorption"	June 2000	48th ASMS Conf. Long Beach, CA
"Metastable Ion Decay of Peptides and Proteins in MALDI TOF-MS Using IR and UV Desorption"	June 2000	48th ASMS Conf. Long Beach, CA
"Fragmentation of Peptides/Proteins In MALDI: A Comparison of IR vs. UV Desorption Wavelengths and Positive vs. Negative Ions"	Sept. 2000	Desorption 2000 St. Malo, France
"Optimizing The Extraction Voltage Waveform To Improve The TLF Focussing Of Ions In Delayed Extraction MALDI"	May 2001	49th ASMS Conf. Chicago, IL
"Ionization In MALDI: Do Solvent Occlusions In Matrix Crystals Play A Role?"	June 2002	50th ASMS Conf. Orlando, FL
"Ionization In MALDI, The Role of Trapped Solvent"	Sept. 1-5, 2002	Desorption 2002 Estes Park, CO

INVITED CONFERENCE PRESENTATIONS

Title	Date	Location
"A Comparison of Deconvolution and Maximum Likelihood Data Processing Techniques Applied to Matrix Assisted Laser Desorption Mass Spectra"	July 1991	Rocky Mountain Conference on Analytical Chemistry Denver, CO

INVITED CONFERENCE PRESENTATIONS (continued)

Title	Date	Location
"Evaluation of an Electrostatic Analyzer Based Time-of-flight Mass Spectrometer"	Aug. 1992	34th Rocky Conference on Analytical Chemistry Denver, CO
"Evaluation of Pulsed Ion Extraction at High Accelerating Fields in a MALDI Time-of-flight Mass Spectrometer"	Aug. 1993	35th Rocky Mountain Conference on Analytical Chemistry, Denver, CO
"Low Temperature Matrix Assisted Laser Desorption Mass Spectrometry"	Aug. 1993	35th Rocky Mountain Conference on Analytical Chemistry Denver, CO
"Matrix-Assisted Laser Desorption: How Soft an Ionization Process?	Aug. 1994	36th Rocky Mountain Conference on Analytical Chemistry Denver, CO
"Recent Advances in Matrix Assisted Laser Laser Desorption/Ionization Time-of-Flight Mass Spectrometry"	Aug. 1995	37th Rocky Mountain Conference on Analytical Chemistry Denver, CO
"High Mass Resolution MALDI TOF Mass Spectrometry"	Nov. 1996	Eastern Analytical Symposium Sommerset, NJ
"New Protein Sequencing Strategies Using MALDI In-Source Decay"	Aug. 1997	38th Rocky Mountain Conference on Analytical Chemistry Denver, CO
"IR-MALDI Employing a Short Pulsewidth Nd:YAG Pumped OPO"	Sept. 1998	Desorption 98 Conf. Angra dos Reis,
"Sequencing Peptides and Proteins by In-Source and Post-Source Decay"	Jan. 1999	HPCE Conference Palm Springs, CA
"A Review Of Current Mechanistic Models Of The MALDI Process And Their Implications For Developing Successful Sample Analysis Protocols"	Jan. 2002	Sanibel Island Conf. Sanibel Island, Fl

"Towards a Unified Matrix-Assisted Laser Desorption/Ionization Mechanism: Implications of IR-MALDI Studies"	Nov. 2002	Eastern Analytical Symposium Somerset, NJ

INVITED SEMINARS

Title	Date	Location
"Laser Desorption Mass Spectrometry of Large Molecules"	Nov., 1989	Dept. of Chemistry Tulane University
"Recent Advances in the Mass Spectrometric Analysis of Biological Molecules"	Oct., 1991	Hybritech, Inc. San Diego, CA
"Recent Advances in the Mass Spectrometric Analysis of High Molecular Weight Materials"	April 1991	Sigma Xi CSU
"Recent Development in Matrix Assisted Laser Desorption Mass Spectrometry"	Oct. 1992	Colorado School of Mines
"Utilization of MALDI Fast Metastable Ion Decay Ions for Peptide/Protein Sequencing"	Aug. 1996	Hewlett Packard Co. Palo Alto, CA
"New Developments in MALDI Time-of-flight Mass Spectrometry"	Nov. 1996	University of Georgia
"IR Vs. UV Lasers For Performing Matrix-Assisted Laser Desorption/Ionization: Practical Aspects and Implications For Ionization Mechanisms"	March 2000	Brigham Young U., Provo, UT

FUNDED RESEARCH GRANTS

Title	Donor	Years	Amount
"Study of the Laser Induced Desorption of Non-volatile Material via Matrix Isolation Fourier Transform Infrared Spectrometry"	CSU Faculty Research Grant	1/1/88 - 12/31/88	$ 3,000
Shell Faculty Development Grant	CSU	6/88 - 6/89	$ 10,000
"Laser Induced Thermospray Ionization for Pulsed Mass Spectrometers"	NIH	9/89 - 9/90	$ 33,228

"Laser Desorption Mass Spectrometry: Effects of Various Matrices and Wavelength"	CSU Faculty Research Grant	1/1/90 - 12/31/90	$ 4,300
"Introduction of Gas Chromatography-Mass Spectrometry in the Undergraduate Curriculum"	NSF	1/1/90 - 6/30/91	$ 61,053
"Fundamental Studies of Matrix Assisted Laser Desorption Mass Spectrometry"	NIH	9/30/92 - 2/28/96	$ 296,141
"Frozen Aqueous Matrices For MALDI Mass Spectrometry	USU Faculty Research Grant	7/1/95 - 6/30/96	$ 14,160
"In-Source Decay MALDI TOF-MS of Peptides"	Hewlett Packard Company	1/1/96 - 10/1/97	$ 10,571
"Matrix-Assisted Laser Desorption - Fundamental Studies"	NIH	1/1/97 - 6/30/01	$ 369,774
"Unrestricted Funds for Matrix-Assisted Laser Desorption Studies"	Perseptive Biosystems	6/01/2000	$ 10,000
"Unrestricted Funds for Matrix-Assisted Laser Desorption Studies"	Perseptive Biosystems	1/01/2002	$ 10,000
"Unrestricted Funds for IR-MALDI Development"	Ciphergen Biosystems	11/01/2002	$ 10,000

DONATED EQUIPMENT FOR SUPPORT OF RESEARCH

Instrumentation Received	Donor	Year	Estimated Value
Computer and electronic measurement equipment	Hewlett Packard Company	1996	$ 20,000
Fourier Transform Mass Spectrometer (FTMS 2000)	Phillips Petroleum Co.	1997	$ 350,000
Quadrupole Mass Spectrometer	Phillips Petroleum Co.	1997	$ 25,000
Voyager MALDI TOF-MS	Perseptive Biosystems	8/2002	$ 100,000

RESEARCH PROPOSALS IN PREPARATION

Title	Donor	Years	Amount
"New MALDI TOF-MS Instrument Designs"	NIH	12/1/03-11/30/05	$ 150,000

PLANNED RESEARCH PROPOSALS

"Fundamentals Studies of Matrix-Assisted Laser Desorption/Ionization"	NSF	1/01/04 - 12/31/06	$ 290,000

PUBLICATIONS

1. R.S. Brown, D.W. Hausler and L.T. Taylor, "Gel Permeation Chromatography of Coal Derived Products with On-Line Infrared Detection", *Anal. Chem.* 52, 1511-1515 (1980).

2. R.S. Brown, D.W. Hausler, R.O. Carter and L.T. Taylor, "Fourier Transform Infrared Spectrometric Detection in the Size Exclusion Chromatographic Separation of Polar Synfuel Material" *Anal. Chem.* 53, 197-201 (1981).

3. R.S. Brown, J.W. Hellgeth, D.W. Hausler and L.T. Taylor, "Coal and Coal Products: Analytical Characterization Techniques", *ACS Symposium Series* 205, 163-183 (1982).

4. R.S. Brown and L.T. Taylor, "Speciation of Intermediate Polar Material in Coal Derived Process Solvents by Liquid Chromatography/Fourier Transform Infrared Spectrometry", *Anal. Chem.* 55, 723-730 (1983).

5. R.S. Brown, J.W. Hellgeth, A.M. Squires, and L.T. Taylor, "The Occurrence and Role of Organometallics in Coal Liquefaction", EPRI Report AP-2980, Project 1696-2 (March, 1983).

6. R.S. Brown and L.T. Taylor, "Microbore Liquid Chromatography with Flow Cell Fourier Transform Infrared Spectrometric Detection", *Anal. Chem.* 54, 1492-1497 (1983).

7. D.A. Laude, G.M. Brissey, C.F. Ijames, R.S. Brown and C.L. Wilkins, "Linked Gas Chromatography/Fourier transform Infrared/Fourier Transform Mass Spectrometry with Integrated Electron Impact and Chemical Ionization", *Anal. Chem.* 56, 1163-1168 (1984).

8. J.W. Hellgeth, R.S. Brown and L.T. Taylor, "Effect of Coal Liquefaction Conditions on the trace Element Content of the Soluble Non-Volatile Product", *Fuel* 63, 453-462 (1984).

9. R.S. Brown and L.T. Taylor, "Detectability of Phenols and Amines by Normal Phase Microbore HPLC-FTIR Employing Highly IR Transparent Solvents", *Chromatographia* 18, 396-400 (1984).

PUBLICATIONS (Continued)

10. D.A. Laude, C.L. Johlman, R.S. Brown, C.F. Ijames and C.L. Wilkins, "Pulsed Valve Chemical Ionization for Gas Chromatography/Fourier Transform Mass Spectrometry", *Anal. Chim. Acta* 178 67-77 (1985).

11. R.S. Brown, J.R. Cooper and C.L. Wilkins, "Lightpipe Temperature and Other Factors Affecting Signal in Gas Chromatography-Fourier Transform Infrared Spectrometry", *Anal. Chem.* 57, 2275-2279 (1985).

12. C.L. Johlman, D.A. Laude, R.S. Brown, and C.L. Wilkins, "Pulsed-Valve Reagent Addition for Chemical Ionization Mass Spectrometry: Mass Measurement Accuracy", *Anal. Chem.* 57, 2726-2728 (1985).

13. D.A. Laude, C.L. Johlman, R.S. Brown and C.L. Wilkins, "Negative Chemical Ionization and Accurate Mass Measurement Applications of a linked Gas Chromatography/Fourier transform Infrared Spectrometry/Fourier transform Mass Spectrometer", *Frens. Z. Anal. Chemie* 324, 839-845 (1986).

14. R.S. Brown, D.A. Weil and C.L. Wilkins, "Laser Desorption-Fourier Transform Mass Spectrometry for the Characterization of Polymers", *Macromolecules* 19, 1255-1260 (1986).

15. D.A. Laude, C.L. Johlman, R.S. Brown, D.A. Weil and C.L. Wilkins, "Fourier Transform Mass Spectrometry: Recent Instrument Developments and Applications", *Mass Spectrom Rev.* 5, 107-166 (1986).

16. R.S. Brown and C.L. Wilkins, "Laser Desorption Fourier Transform Mass Spectrometry of Chlorophyll A and Chlorophyll B", *J. Am. Chem. Soc.* 108, 2447-2448 (1986).

17. I.C. Bowater, R.S. Brown, J.R. Cooper and C.L. Wilkins, "Maximum Absorbance Algorithm for Reconstruction of Gas Chromatograms from Gas Chromatography/Infrared Spectrometry Data", *Anal. Chem.* 58, 2195-2199 (1986).

18. E.S. Schmidt, T.C. Bruice, R.S. Brown and C.L. Wilkins, "Oxygen Transfer from an Ozonide to Tetraphenyl-Porphyrin Chromium (III) Chloride", *Inorg. Chem.* 25, 4799-4800 (1986).

19. R.S. Brown and C.L. Wilkins, "Laser Desorption Fourier Transform Mass Spectrometry of Synthetic Porphyrins", *Anal. Chem.* 58, 3196-3199 (1986).

20. R.S. Brown and C.L. Wilkins, "Current Status of High Mass Analysis by Fourier Transform Mass Spectrometry", *Mass Spectrometry in the Analysis of Large Molecules*, Edited by C.J. McNeal, John Wiley and Sons, Ltd. (1986).

21. R.S. Brown and C.L. Wilkins, "Analytical Applications of Laser Desorption Fourier Transform Mass Spectrometry", *ACS Symposium Series* 359, Chapter 8 (1987).

PUBLICATIONS (Continued)

22. R.S. Brown and C.L. Wilkins, "A Cryogenically Cooled Interface for Gas Chromatography/Fourier Transform Infrared Spectrometry", *Anal. Chem.* 60, 1483-1488 (1988).

23. R.S. Brown and C.L. Wilkins, "Laser Mass Spectrometry: Application to Polymer Analysis", (Chapter 1 in *Applications of Lasers in Polymer Science and Technology*, Vol. 4, 1990, CRC Press, Boca Raton, FL).

24. R.S. Brown and N.L. Gilfrich, "Fourier Transform Infrared Spectrometry Coupled with Cryogenic Trapping for the Study of Laser Desorbed Neutrals", *Appl. Spectrosc.* 44, (8), 1399-1404 (1990).

25. R.S. Brown and J.J. Lennon, "Factors Affecting Sensitivity in Lightpipe Gas Chromatography Fourier Transform Infrared Spectrometry Interfaces", *Appl. Spectrosc.* 45 (4), 666-672 (1991).

26. R.S. Brown and N.L. Gilfrich, "Design and Performance of a Matrix Assisted Laser Desorption Time-of Flight Mass Spectrometer Utilizing a Pulsed Nitrogen Laser", *Anal. Chim. Acta.* 248, 541-552 (1991).

27. R.S. Brown and N.L. Gilfrich, "Optimizing Signal and Mass Resolution for Matrix Assisted Laser Desorption Utilizing a Linear Time-of-flight Mass Spectrometer" *Rapid Comm. in Mass Spectrom.* 6(11), 697 (1992).

28. R.S. Brown and N.L. Gilfrich, "Ion Detection limitations to Mass Resolution in Matrix Assisted Laser Desorption Time-of-flight Mass Spectrometry" *Rapid Comm. in Mass Spectrom.* 6(11), 690 (1992).

29. R.S. Brown and N.L. Gilfrich, "Maximum Likelihood Restoration Data Processing Techniques Applied to Matrix Assisted Laser Desorption Mass Spectra",*Appl. Spectrosc.* 47(1), 103 (1993).

30. R.S. Brown and J.J. Lennon, "Mass Resolution Improvement by Incorporation of Pulsed Ion Extraction in a Linear Time-of-Flight Mass Spectrometer", *Anal. Chem.*, 67(13), 1998 (1995).

31. B.L. Carr and R.S. Brown, "Matrix Isolation/Fourier Transform Infrared Spectrometry of Laser-Desorbed Species", *Appl. Spectrosc.*, 49(7), 955 (1995).

32. R.S. Brown and J.J. Lennon, "Sequence Specific Fragmentation of Matrix Assisted Laser Desorbed Protein/Peptide Ions", *Anal. Chem.*, 67(21), 3990 (1995).

33. R.S. Brown, B.L. Carr and J.J. Lennon, "Factors Influencing the Observed Fast Fragmentation of Peptides in Matrix Assisted Laser Desorption", *JASMS*, 7, 225 (1996).

34. R.S. Brown, J. Feng and D.C. Reiber, "Further Studies of In-Source Fragmentation of Peptides in Matrix-Assisted Laser Desorption/Ionization", *Int. J. Mass Spectrom. Ion*

PUBLICATIONS (Continued)

Processes, 169-170, 169 (1997).

35. D.C. Reiber, T.A. Grover and R.S. Brown, "Identifying Proteins Using Matrix-Assisted Laser Desorption/Ionization In-Source Fragmentation Data Combined with Database Searching" *Anal. Chem.*, 70(4), 673 (1998).

36. D.C. Reiber, S. Weinberger, J. Kenny, J. Bailey and R.S. Brown, "Unknown Peptide Sequencing Using Matrix-Assisted Laser Desorption/Ionization and In-Source Decay" *Anal. Chem.*, 70(6), 1214 (1999).

37. E. E. Durrant and R.S. Brown, "Metastable Ion Decay of Peptides and Proteins in MALDI TOF-MS Using IR and UV Desorption", *The Proceedings of the 47thASMS Conference on Mass Spectrometry and Allied Topics*", 1058, 1999.

38. E. E. Durrant and R.S. Brown, "A Comparison of IR-MALDI and UV-MALDI In-Source Decay of Peptides and Proteins", *The Proceedings of the 47th ASMS Conference on Mass Spectrometry and Allied Topics*", 1116, 2000.

39. C.R. LaPerriere and R.S. Brown, "Use of a Second Extraction Pulse to Improve the TLF Focussing of Ions in Delayed Extraction MALDI", *The Proceedings of the 48th ASMS Conference on Mass Spectrometry and Allied Topics*", 1537, 2000.

40. C.R. LaPerriere and R.S. Brown, "Optimizing The Extraction Voltage Waveform To Improve The TLF Focussing Of Ions In Delayed Extraction MALDI" *The Proceedings of the 49th ASMS Conference on Mass Spectrometry and Allied Topics*", 2001.

SUBMITTED MANUSCRIPTS

40. J. Feng, E. E. Durrant and R.S. Brown, "Synthesis of Various Substituted Cinnamic Acids and Their Application for Matrix-Assisted Laser Desorption/Ionization of Peptides and Proteins", Submitted for publication in the *Journal of Mass Spectrometry* (revised and resubmitted).

41. J. Feng and R.S. Brown, "Factors Affecting the Extent of Multiple Protonation of Protein Analytes in Matrix-Assisted Laser Desorption/Ionization Mass Spectrometry", Submitted for publication in the *Journal of Mass Spectrometry (under revision).*

42. B. Bennett;, V. D'souza, R.S. Brown, R.C. Holz, "The Anti-Angiogenesis Agent Fumagillin does not Coordinate to the Dinuclear Active Site of the Methionyl Aminopeptidase from Escherichia coli." Submitted for publication in the *Journal of the American Chemical Society.*

MANUSCRIPTS IN PREPARATION

43. J. Feng and R.S. Brown, "Development of New Co-Matrix Systems for MALDI Mass Spectrometry", To be submitted for publication in the *Journal of the American Society for Mass Spectrometry.*

45. E. E. Durrant and R.S. Brown, "IR-MALDI Employing a Short Pulsewidth Nd:YAG Pumped OPO", To be submitted for publication in *Analytical Chemistry.*

MANUSCRIPTS PLANNED

46. E. E. Durrant and R.S. Brown, "Effect of Desorption Wavelength on Post-Source Ion Decay in IR-MALDI", To be submitted for publication in *Journal of the American Society for Mass Spectrometry.*

47. E. E. Durrant and R.S. Brown, "Comparison of In-Source Decay Fragmentation Pathways in UV-MALDI and IR-MALDI", To be submitted for publication in *Journal of the American Society for Mass Spectrometry.*

BOOK REVIEWS

1. Review of "Practical Fourier Transform Infrared Spectrometry: Industrial and Laboratory Chemical Analysis", *J. Am.. Chem.. Soc.* 112, 6454 (1990).

2. Review of "Time-of-Flight Mass Spectrometry and Its Applications", *J. Am.. Soc. Mass Spectrom..* 5, 949, (1994).

STUDENT RESEARCHERS SUPERVISED (1987 - Present)

GRADUATE STUDENTS

Nancy Lynn Gilfrich, Ph.D. - May 1992 (CSU)
Thesis Title: "X-ray Fluorescence Macroprobe Analysis of Slates and Matrix Assisted Laser Desorption of Biomolecules"

Bryan Carr, Ph.D. - December 1995 (CSU)
Thesis Title: "Fourier Transform Infrared Spectrometry/Matrix Isolation of Laser Desorbed Species"

John Lennon, Ph.D. - September 1996 (CSU)
Thesis Title: "Delayed Pulsed Ion Extraction MALDI Linear Time-of-Flight Mass Spectrometry"

Duane Reiber, Ph.D. - June 1999 (USU)
Thesis Title: "The Utility of Hydroxy Substituted Benzophenones as MALDI Matrices and Peptide/Protein Sequencing Using Delayed Extraction MALDI Time-of-flight Mass Spectrometry and In-Source Fragmentation"

GRADUATE STUDENTS (Continued)

Jinhua Feng, Ph.D. - June 1999 (USU)
Thesis Title: "Synthesis and Characterization of Substituted Cinnamic Acid Derivatives as Matrices for Matrix-Assisted Laser Desorption/Ionization Mass Spectrometry"

Edward Durrant, Ph.D. - June 2001(USU)
Thesis Title: "Comparison of Ultraviolet and Infrared Matrix-Assisted Laser Desorption Ionization Time-of-Flight Mass Spectrometry"

Craig LaPerriere	MS Candidate (Writing thesis – Expected Graduation Spring 2003)
Thesis Title:	"Dynamic Delayed Extraction For MALDI TOF-MS"

CURRENT UNDERGRADUATE RESEARCH STUDENTS

Nate Maeser	USU ChemistryUndergraduate Student (BS Expected Spring 2003)

FORMER UNDERGRADUATE RESEARCH STUDENTS

John Jones	M.S. Oregon State University (1997)
Peter Staples	Exchange student from Australia
John Lane	Employed by Eli Lilly and Co., St. Louis, MO
Todd Rhea	Employed by Spectrace, Ft. Collins, CO
Dawn Richards	Present Status Unknown
Dan Meyers	Employed by EPA, Denver, CO

PROFESSIONAL SERVICE RELATED ACTIVITIES

NATIONAL SYMPOSIA ORGANIZED

1. "Laser Desorption Ionization - Fundamentals" at the 43rd ASMS Conference on Mass Spectrometry and Allied Topics, May 24, 1995, Atlanta, GA. (Organizer and Session Chair).

2. "MALDI Design and Fundamentals" at the 45th ASMS Conference on Mass Spectrometry and Allied Topics, June 5, 1997, Palm Springs, CA. (Co-Organizer and Session Co-Chair).

3. General Chairman and Program Organizer for the 6th International Desorption Conference (Desorption 2002) held Sept. 1-5, 2002 in Estes Park, CO.

4. Program Organizer for 2002 EAS Analytical Award Symposium Honoring Prof.

Charles Wilkins. Held at EAS meeting, November, 2002, Sommerset, NJ.

OUTSIDE CONSULTING

1. Consultant to Tulane University on the purchase of a high resolution mass spectrometer (Oct. 1989 - June 1990).
2. Consultant to Hybritech, Inc. (Sept. 1991 - June 1994).
3. Consultant to DuPont (Oct. 1994 - Present).
4. Consultant to Hewlett Packard Co. (Jan. 1996 - Oct. 1997).
5. Consultant to Phillips Petroleum Co. (Aug. 1997 - 2001).
6. Consultant to PE Biosystems (June 1999 - Present).
7. Consultant to Ciphergen Biosystems (July 2002 – Present)

OUTSIDE STUDY SECTIONS AND REVIEW PANELS

1. National Science Foundation, Directorate for Education and Human Resources, Instrumentation and Laboratory Improvement Program, panel member, January 1991.
2. National Science Foundation, Directorate for Education and Human Resources, Instrumentation & Laboratory Improvement Program, panel chairman, January 1992.
3. National Science Foundation SBRI review panel member, July 1995.
4. National Science Foundation Major Research Instrumentation Program (Bio Instrumentation) review panel member (appointed March 1997 through April 1999).
5. National Institutes of Health - Ad hoc member of Metallobiochemistry Study Section - Spring 1999.
6. National Institutes of Health - Ad hoc member of Metallobiochemistry Study Section, Special Emphasis Panel (BMT SEP) - February 2000.
7. National Institutes of Health - Ad hoc member of Metallobiochemistry Study Section, Special Emphasis Panel (BMT SEP) - June 2000.
8. National Institutes of Health - Ad hoc member of Chemical Instrumentation Special Study Section - Nov. 13, 2000.

PEER REVIEWER FOR THE FOLLOWING AGENCIES

1. NSF (Various divisions including: Chemistry, Biological Instruments, and Chemical Instrumentation)
2. NIH (Outside Reviewer for Metallobiochemistry Study Section)
3. DOD (Army)
4. Environmental Protection Agency
5. DOE

PEER REVIEWER FOR FOLLOWING JOURNALS

1. Analytical Chemistry
2. Journal of the American Society for Mass Spectrometry
3. Analyst
4. Applied Spectroscopy
5. Journal of Mass Spectrometry
6. International Journal of Mass Spectrometry and Ion Processes
7. Rapid Communications in Mass Spectrometry

United States Patent [19]

Beavis et al.

[11] **Patent Number: 5,045,694**

[45] **Date of Patent: Sep. 3, 1991**

[54] **INSTRUMENT AND METHOD FOR THE LASER DESORPTION OF IONS IN MASS SPECTROMETRY**

[75] Inventors: **Ronald C. Beavis; Brian T. Chait,** both of New York, N.Y.

[73] Assignee: **The Rockefeller University,** New York, N.Y.

[21] Appl. No.: **413,321**

[22] Filed: **Sep. 27, 1989**

[51] **Int. Cl.**[5] **B01D 59/44; H01J 49/00**

[52] **U.S. Cl.** ..... **250/287;** 250/288; 250/282; 250/423 P

[58] **Field of Search** ..... 250/287, 288, 282, 423 P

[56] **References Cited**

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Karas et al., UV Laser Matrix Desorption/Ionization . . . 100,000 Dalton Range, (1989), pp. 231-242.

Hillenkamp et al., Matrix Assisted UV-Laser Desorption/Ionization, pp. 1-9.

Hillenkamp et al., On Popping Corn, Erupting Vulcanos, Tasting Wine, Massive Proteins and Related Matters, 1989, pp. 1-8.

Karas et al., Laser Desorption/Ionization Mass Spectrometry of Proteins of Mass 100,000 to 250,000 Dalton, Angewandte Chemie, Jun. 1989, pp. 760-761.

Karas et al., Ultraviolet-Laser Desorption/Ionization Mass Spectrometry of Femtomolar Amounts of Large Proteins, vol. 18 (1989), pp. 841-843.

Tanaka et al., Detection of High Mass Molecules by Laser Desorption Time-of-Flight Mass Spectrometry.

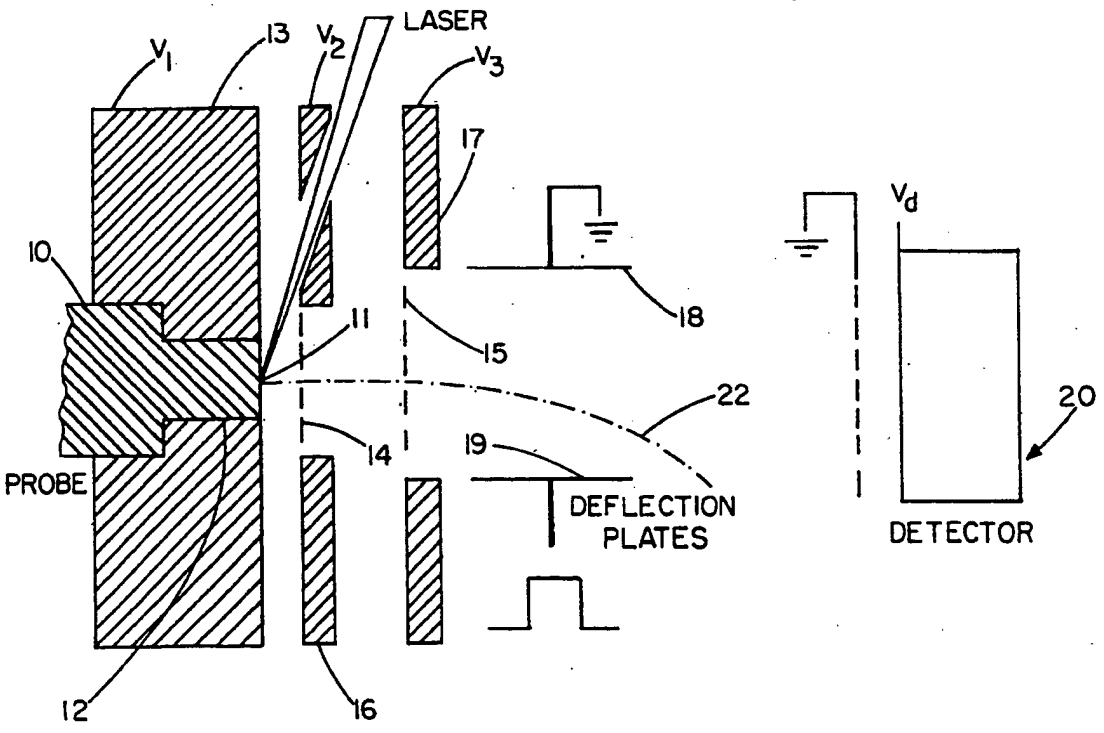
Primary Examiner—Bruce C. Anderson

Attorney, Agent, or Firm—Browning, Bushman, Anderson & Brookhart

[57] **ABSTRACT**

In mass spectrometry, a time of flight (TOF) mass spectrometer is used to measure the mass spectrum of organic molecules of mass ranging from 200 Dalton to greater than 200,000 Dalton. Ions from the sample are desorbed by striking the probe tip with laser pulses in a spot size, on the tip, in the range of 0.03-3.0 mm^2. The time of flight of the ions is measured and displayed with a resolution of the ion molecular signal in the range of 300-500 full width at half-maximum definition (FWHM).

24 Claims, 2 Drawing Sheets



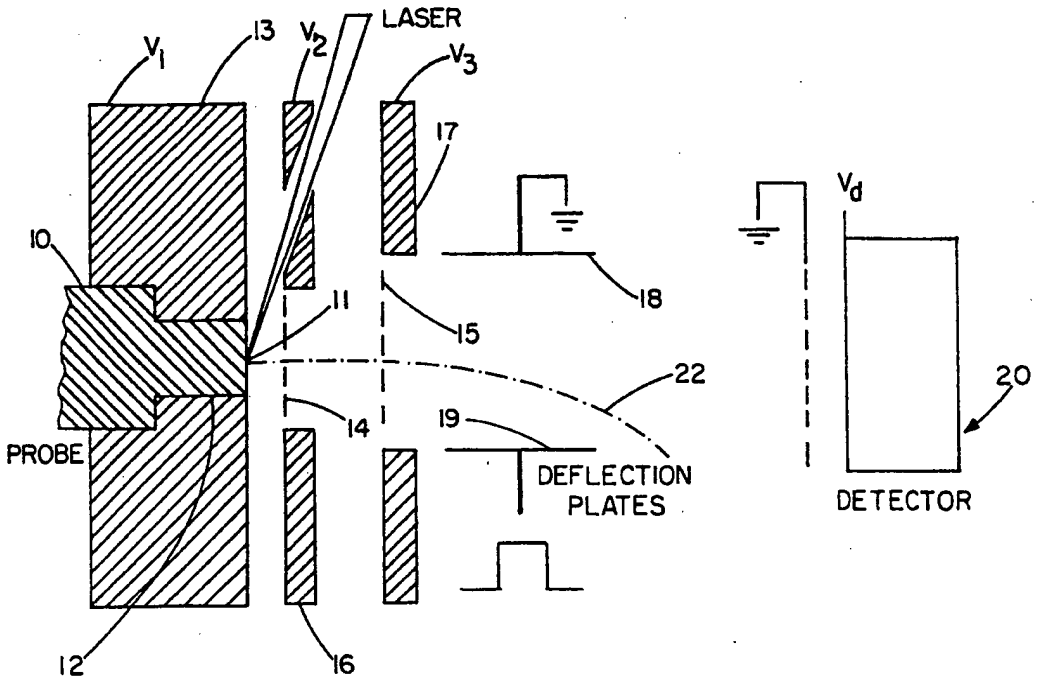

LASER
V_1
13
V_2
V_3
17
10
11
15
18
V_d
22
20
14
19
PROBE
DEFLECTION PLATES
DETECTOR
12
16

FIG. 1

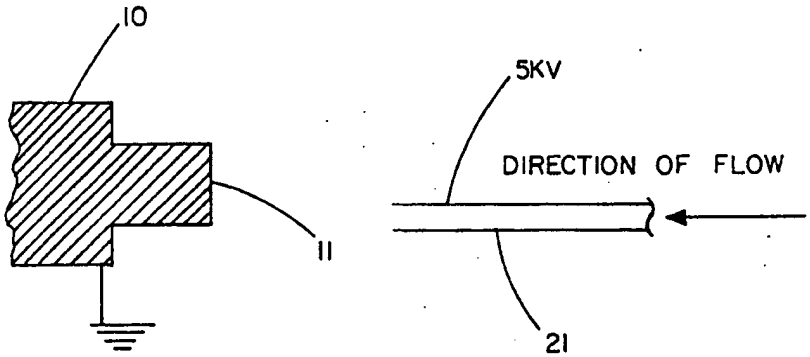

10
5KV
DIRECTION OF FLOW
11
21

FIG. 3

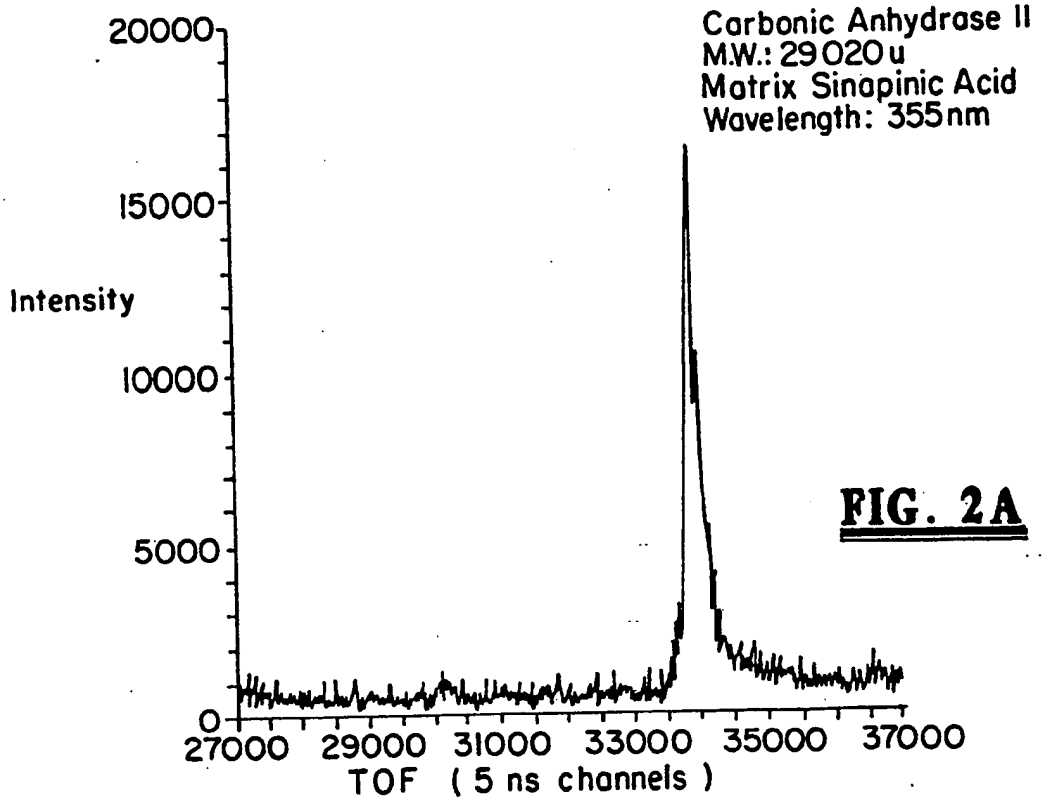

Carbonic Anhydrase II
M.W.: 29020u
Matrix Sinapinic Acid
Wavelength: 355nm
Intensity
20000
15000
10000
5000
0
27000
29000
31000
33000
35000
37000
TOF (5 ns channels)

FIG. 2A

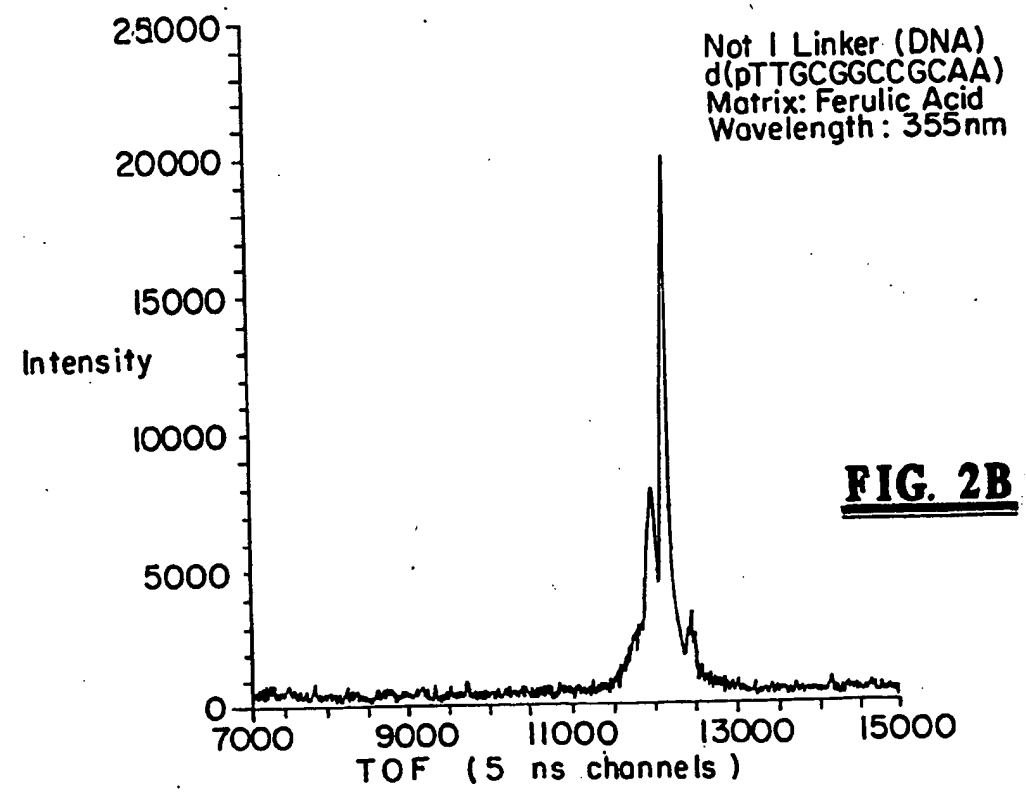

Not I Linker (DNA)
d(pTTGCGGCCGCAA)
Matrix: Ferulic Acid
Wavelength : 355nm
Intensity
25000
20000
15000
10000
5000
0
7000
9000
11000
13000
15000
TOF (5 ns channels)

FIG. 2B

INSTRUMENT AND METHOD FOR THE LASER DESORPTION OF IONS IN MASS SPECTROMETRY

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to mass spectrometry and more particularly to the laser desorption of very large organic molecules using a time of flight (TOF) mass spectrometer.

2. Description of the Related Art

Mass spectrometry is an analytical technique for the accurate determination of molecular weights, the identification of chemical structures, the determination of the composition of mixtures and quantitative elemental analysis. For example, it is possible to accurately determine the molecular weights of organic molecules. It is also possible to determine the structure of the organic molecules based on the fragmentation pattern of the ion formed when the molecule is ionized. A quantitative elemental analysis of organic molecules and compounds requires obtaining precise mass values from a high resolution mass spectrometer.

One type of mass spectrometer obtains a mass spectrum by passing the ions (electrically charged atoms or molecules) through a magnetic field. The ions form a beam which, when they are of different masses, are deflected through different angles by the magnetic field. The magnetic field is varied (swept) and, at each field strength, ions pass through precision slits to be measured by an electrical detector (electrometer). However, primarily due to the limitations of magnetic field strength, it is impractical to measure molecules having a mass-to-charge ratio (m/Z) greater than about 15,000.

The organic molecules of greater mass which are non-volatile and thermally labile (decomposed by heat) are of great medical and commercial interest, as they include, for example, proteins, DNA, oligosaccharides, commercially important polymers and pharmaceuticals.

It has been suggested, in a series of articles published by "Hillenkamp-Karas", cited below, that large organic molecules, of about 10,000–100,000 Daltons, may be analyzed in a time of flight (TOF) mass spectrometer. Those articles describe that the molecules of interest are dissolved in an aqueous solution of nicotinic acid, in a ratio of one molecule of interest to 1000 nicotinic acid molecules. The solution is dried and placed on a sample probe tip that is inserted into a TOF mass spectrometer. The dried material on the tip is searched, using a microscope, for a suitable spot, and that spot is activated by a laser beam ("microprobe"). The laser beam wavelength is in the UV (ultraviolet) region (266 nm wavelength) and the beam size at the tip is 8 um diameter (Hillenkamp 1) or 10–50 um (Karas, 2,3). The molecules are desorbed and ionized by the laser beam and are formed into beams by a series of electrodes creating an electric field, typically of 1000 volts/cm. The ion beam is directed down a tube which is a vacuum chamber (spectrometer tube), generally having an equilibrium pressure in the order of 10^{-6} mm mercury. Ions of different masses require different times to transverse the spectrometer tube. The time the tip (target) is struck with a laser pulse is taken as time zero and the various times the ions arrive at the opposite end (the ion detector) are measured and displayed generally on a graph (the mass spectrum).

The frequency of the laser is chosen to match the absorption frequency of the solid matrix, principally of nicotinic acid, which exhibits strong absorption at 266 nm wave length. The laser pulses, of 15 ns pulse width and 266 nm wavelength, are obtained from a frequency quadrupled Q-switched ND-YAG solid crystal laser instrument.

The "Hillenkamp-Karas" articles are the following:

1. Hillenkamp, "Laser Desorption Mass Spectrometry: Mechanisms, Techniques and Applicatons"; *Bordeaux Mass Spectrometry Conference Report*, 1988. pages 354–362.

2. Karas and Hillenkamp, "Ultraviolet Laser Desorption of Proteins Up to 120,000 Daltons", *Bordeaux Mass Spectrometry Conference Report*, 1988, pages 416,417.

3. Karas and Hillenkamp, "Laser Desorption Ionization of Proteins With Molecular Masses Exceeding 10,000 Daltons", *Analytical Chemistry*, 60, 2299, July 1988.

4. Karas, Ingendoh, Bahr and Hillenkamp, "UV-Laser Desorption/Ionization Mass Spectrometry of Femtomol Amounts of Large Proteins", *Biomed. Environ. Mass Spectrum*. (in press)

Although the previously described Hillenkamp-Karas articles are a real advance in the field, there are a number of problems and limitations to the methods.

The resolution of the mass spectrum is not as sharp as is possible, at much lower molecular weights. with magnetic field mass spectrometry. The Hillenkamp-Karas graphs show what appear to be a broad envelope of mass weights rather than the sharp peaks. which are desired. The work so far published by Hillenkamp and Karas on nicotinic acid assisted UV laser desorption shows spectral peaks with resolutions of less than about 50 Full Width at Half-Maximum definition (FWHM).

In addition, the procedure is time-consuming and costly. One must obtain a suitable spot on the tip using a microscope, by trial and error, and a number of attempts may be made before a successful spot is found. The instruments required to be used (laser microprobes and LAMMA) are relatively costly and complex. They have only studied positive ions, although negative ions sometimes provide complementary and/or unique information.

The wavelength published by Karas-Hillenkamp, in some cases, presents problems as to some molecules because that wavelength causes undesirable fragmentation of the molecule. It is difficult to simply change the wavelength with the teaching of the Karas-Hillenkamp articles, because the matrix (nicotinic acid) will only effectively absorb laser energy in a restricted range of wavelengths (below about 300 nm).

The use of laser beams in time of flight mass spectrometers is shown, for example, in U.S. Pat. Nos. 4,694,167; 4,686,366 and 4,295,046, incorporated by reference herein.

OBJECTIVES OF THE INVENTION

It is an objective of the present invention to provide a method and apparatus in mass spectrometry which will provide for the analysis of molecules whose mass is in the range of 200–200,000 Dalton, or greater, and including large non-volatile bio-organic molecules.

It is a further objective of the present invention to provide such a mass spectrometry instrument and method which is relatively simple to operate, permits rapid preparation of samples, provides results quickly, and is relatively low in cost.

It is a further objective of the present invention to provide such a mass spectrometry instrument and method which may be used to analyze negative ions as well as positive ions.

It is a further objective of the present invention to provide such a mass spectrometry instrument and method which will cause relatively less fragmentation of the molecules.

It is a further objective of the present invention to provide such a mass spectrometry instrument and method which may be used with relatively small samples, of the order of 0.01 picomole, and which will provide reproducible sample layers.

It is a further objective of the present invention to provide such a mass spectrometry instrument and method which are able to analyze samples which are mixtures of materials.

It is a further objective of the present invention to provide such a mass spectrometry instrument and method which are able to analyze large organic molecules in addition to proteins, for example, DNA, polymers, glycolipids, glycoproteins, oligosaccharides, etc.

SUMMARY OF THE INVENTION

In accordance with the present invention, there is provided a system and method in mass spectrometry for the mass analysis of non-volatile large organic molecules in the range of 200–200,000 Dalton, or greater.

The instrument is a time of flight (TOF) mass spectrometer. The organic molecule material, to be analyzed, is dissolved in a solution containing a matrix, preferably a cinnamic acid analogue such as caffeic acid, syanpinic acid and ferulic acid. In one method, the matrix material and sample is deposited as a thin layer on the metal tip of a probe. The probe is inserted into the mass spectrometer and the tip is irradiated with a UV laser beam at the wavelength of 200–600 nanometers, preferably 330–550 nm, and pulses of 1–20 ns pulse width, to form a relatively large laser spot on the tip, in the range of 0.03–3.0 mm^2 and most preferably in the range of 0.1–1.0 mm^2.

The spectrometer has a plate and gridded electrodes to form an electric field which is switched to be either positive or negative and to thereby form a beam of either positive or negative ions released by the laser. The times of flight of the ions are displayed on a graph exhibiting the relatively high resolution and low noise possible using the present invention.

BRIEF DESCRIPTION OF THE DRAWINGS

Other objectives of the present invention will be apparent from the following detailed description taken in conjunction with the accompanying drawings, in which:

FIG. 1 is a diagram of the system of the present invention;

FIG. 2A is a mass spectrum of carbonic anhydrase obtained according to the present invention;

FIG. 2B is a mass spectrum of Not 1 Linker DNA obtained according to the present invention; and

FIG. 3 is a side cross-sectional view of the parts used in the electrospray process.

DETAILED DESCRIPTION OF THE INVENTION

The following specific description is of a suitable embodiment of the present invention and its materials, voltages, etc. is illustrative of the invention and not intended to be limiting as to the scope of the invention.

The present invention utilizes a time of flight (TOF) mass spectrometer of the type illustrated in FIG. 1. The probe **10** is of platinum metal and has a flat face **11** which is round in cross-section and has a 2 mm diameter. The probe **10** is manually inserted and may be manually removed from the round bore **12** of the metal wall **13** of the spectrometer. The wall **13** is at voltage V_1.

The ions extracted from the face **11** of the probe are attracted and pass through the grid covered holes **14, 15** in the metal plates **16, 17** respectively. The plates **16, 17** are at voltages V_2 and V_3. Preferably V_3 is at ground and V_1 and V_2 are varied to set the accelerating electrical potential, which typically is in the range of 15,000–50,000 volts. A suitable voltage $|V_1-V_2|$ is 5000 volts and a suitable range of voltages $|V_2-V_3|$ is 10,000 to 45,000 volts.

The low weight ions are generally numerous and may swamp the detector **20**. They are almost entirely prevented from reaching the detector **20** by the deflection plates **18, 19**. The ions travel as a beam between the deflection plates **18, 19**, which suitable are spaced 1 cm. apart and are 3–10 cm long. Plate **18** is at ground and plate **19** receives square wave pulses, for example, at 700 volts with a pulse width in the order of 1 microsecond after the laser strikes the tip. Such pulses suppress the unwanted low mass ions, for example, those under 10,000 Dalton, by deflecting them, as shown by **22**, so that the low weight ions do not reach the detector **20**, while the higher weight ions pass between the plates **18, 19** after the pulse is off, so they are not deflected, and are detected by detector **20**.

An ion detector **20** is positioned at the end of the spectrometer tube and has its front face maintained at voltage V_d. The gain of the ion detector **20** is set by V_d which typically is in the range of -1500 to -2500 volts. The detector is a chevron-type tandem microchannel plate array.

The spectrometer tube is straight and provides a linear flight path, for example, ½–4 meters in length, preferably about two meters in length. The ions are accelerated in two stages and the total acceleration is in the range of about 15,000–50,000 volts, positive or negative.

The spectrometer is held under high vacuum, typically 10 μPa, which may be obtained, for example, after 2 minutes of introduction of the sample.

The face **11** of the probe is struck with a laser beam to form the ions. Preferably the laser beam is from a solid laser. A suitable laser is an HY-400 Nd-YAG laser (available from Lumonics Inc., Kanata (Ottawa), Ontario, Canada), with a 2nd, 3rd and 4th harmonic generation/selection option. The laser is tuned and operated to produce maximum temporal and energy stability. Typically, the laser is operated with an output pulse width of 10 ns and an energy of 15 mJ of UV per pulse. To improve the spatial homogeneity of the beam, the amplifier rod is removed from the laser.

The output of the laser is attenuated with a 935-5 variable attenuator (available from Newport Corp., Fountain Valley, Calif.), and focused onto the sample on the face **11**, using a 12-in. focal length fused-silica lens.

The incident angle of the laser beam, with respect to the normal of the probe's sample surface, is 70°. The spot illuminated on the probe is not circular, but a strip of approximate dimensions 100×300 um (measured by burn marks on paper). The start time for the data system

(i.e., the time the laser actually fired) is determined using a beam splitter and a P5-01 fast pyroelectric detector (available from Molectron Detector Inc., Campbell, Calif.). The laser is operated in the Q switched mode, internally triggering at 5 Hz, using the Pockels cell Q-switch to divide that frequency to a 2.5 Hz output.

The data system for recording the mass spectra produced is a combination of a TR8828D transient recorder and a 6010 CAMAC crate controller (both manufactured by Lecroy, Chestnut Ridge, N.Y.). The transient recorder has a selectable time resolution of 5–20 ns. Spectra may be accumulated for up to 256 laser shots in 131,000 channels, with the capability of running at up to 3 Hz. The data is read from the CAMAC crate using a Proteus IBM AT compatible computer. During the operation of the spectrometer, the spectra (shot-to-shot) may be readily observed on a 2465A 350 MHz oscilloscope (available from Tektronix, Inc., Beaverton, Oreg.).

This linear TOF system may be switched from positive to negative ions easily and both modes may be used to look at a single sample. The sample preparation was optimized for the production of homogeneous samples in order to produce similar signals from the entire face of the probe tip. The preferred preparation dissolves less than 0.2 g/L of the sample in a 5–10 g/L solution of matrix in water (or 1:1, water+ethanol) and deposits 0.5 μL of the solution on the probe tip.

Compounds useful as matrices for the practice of this invention include organic compounds which absorb above the region at which the DNA bases absorb. Therefore, they should absorb above 300 nm, preferably above 330 nm. As a matter of convenience, it is preferred to utilize compounds which absorb at about 355 nm or higher. The compounds should preferably be solids so that they do not volatilize under the conditions of use. They should not react with DNA under the conditions of use, nor should they decompose to give compounds which do react with DNA.

The presently preferred compounds are cinammic acid derivatives such as ferulic, caffeic and syanpinic acid, all of which are substituted in the phenyl ring with activating groups. Cinammic acid derivatives which absorb above 300 nm and are substituted on the phenyl ring with hydroxyl, alkoxyl, amino, aklylamino, lialkylamino groups in which the alkyl group is preferably methyl or ethyl, but may contain up to six or more carbon atoms are useful.

Those skilled in the art can readily conceive of other compounds which will meet the criteria of this invention. For example, compounds which absorb well above 300 nm and even into the visible or infrared regions of the ulispectrum may be employed. Such compounds may be considered as "based" on cinnamic acid but with longer coordination chains. These would include the α- and B-naphthalene analogues of cinnamic acid, or analogs of these compounds in which the coordination chain of the aliphatic group is extended. Such compounds might be substituted with activating groups. Heterocyclic compounds with the appropriate properties are also included within the scope of the invention.

In addition, the following are suitable matrix materials, particularly from non-DNA organic molecules:

3-Pyridinecarboxylic acid
2-Pyrazinecarboxylic acid
Thymine
3-Methoxy, 4-hydroxybenzoic acid
Thiourea

These suitable matrix materials, listed above, are further described in "Factors Affecting The Ultraviolet Desorption of Proteins", Beavis and Chait, *Rapid Comm. in Mass Spectrometry*, Vol. 3, No. 7 (1989), incorporated by reference herein.

In one method of sample preparation, the droplets of the sample are deposited on the tip face **11** by electrospray (electrodeposition), see FIG. **3**. The matrix material, in this technique, is preferably ferulic acid. The tip is grounded and an electric field, typically of 5000 volts, is created by bringing a charged metal capillary tube **21**, through which the matrix material flows, to within 2 cm of the tip face **11**. Droplets of the matrix material are attracted to the tip face, i.e., are sprayed thereon, forming a dry, thin, evenly spread layer on the tip face. Then a small quantity, in the order of about 1 p mol, of the organic molecule sample of interest, dissolved in a solvent, is applied to the matrix material layer and dried by a stream of air over the tip.

An alternative sample preparation method is to dissolve the organic molecule in an appropriate solvent and mix with a matrix material, for example, a cinnamic acid analogue. A suitable ratio of organic molecule to matrix is 1:10,000. That mixture of solvent and matrix material is applied to the probe tip and dried with an air stream.

The sensitivity of this technique is very high for proteins. With a typical sample loading of 0.1–20 p mol of analyte on the probe tip (3 mm^2) good signals were observed. For most peptides, the optimum signal was produced with a sample coverage of <2 pmol/mm^2 on the probe. There should be a 10^3–10^4 molar excess of matrix for optimum detection.

Preferably the laser beam is operated in the UV region or visible region in the range of 320 nm to 600 nm. At laser wavelengths over 300 nm the organic molecules of interest do not absorb the laser energy and are not fragmented, which is highly desirable. A relatively inexpensive nitrogen laser may be used which produces UV at 337 nm or a dye laser may be used. With the ferulic, syanpinic or caffeic acid matrix materials, a satisfactory wavelength, obtainable with the 3rd harmonic from the solid crystal laser described above, is 355 nm.

FIG. **2A** is a graph of intensity vs. time of flight of the pseudomolecular-ion region of a TOF mass spectrum of the organic molecule carbonic anhydrase **11** from a syanpinic acid matrix at 355 nm wavelength.

FIG. **2B** is a similar graph of Not 1 Linker (DNA) in which the matrix is ferulic acid and the wavelength is 355 nm.

What is claimed is:

1. An instrument system in mass spectrometry to measure the mass of organic molecules including:

(a) a time of flight mass spectrometer means to analyze the mass of said molecules, including a spectrometer tube, vacuum means to apply a vacuum to the tube, electrical potential means within the tube to apply an accelerating electrical potential, and a probe having a tip face, said probe being removably inserted into said spectrometer means;

(b) laser beam means to produce a laser beam directed at said tip and providing a laser spot on the said tip face having an area in the range of from 0.1–1.0 mm^2 to desorb said organic molecules;

(c) detector means to detect the mass weights with a resolution of the peaks of the ion molecular signals

of higher than 50 full width at half-maximum definition (FWHM); and

(d) deflection means comprising a pair of spaced-apart deflection electron plates within said spectrometer tube forming an electrical field between the plates to deflect low mass ions of less than 10,000 Dalton so that they do not reach the detector means.

2. A system as in claim 1 and further including a sample means comprising an organic molecule material of mass weight of over 10,000 Dalton in a matrix of a heat absorbent material on said tip face.

3. A system as in claim 1 wherein the organic molecules are absorbed in a thin, evenly coated layer of matrix material on the tip face.

4. A system as in claim 3 wherein the mole ratio of organic molecules to matrix material is in the range of 1:100 to 1:10,000.

5. A system as in claim 1 wherein the organic molecules are absorbed in an electro-deposited layer of matrix material covering the tip face.

6. A system as in claim 1 wherein the accelerating electrical potential produces negative ions of the molecules.

7. A system as in claim 2 wherein the laser has an output pulse width in the 1–10 ns range.

8. A system as in claim 1 wherein the laser has a wavelength in the range of 200–600 nanometers.

9. A system as in claim 1 wherein the laser has a wavelength in the range of 330–550 nanometers.

10. A method in mass spectrometry to measure the mass of organic molecules of over 10,000 Dalton mass weight with improved resolution, including the steps of:

(a) forming a thin and even layer on the probe tip face of the organic molecules absorbed in a matrix of light-absorbent material;

(b) placing the probe into one end of a time of flight mass spectrometer and applying a vacuum and an electric field to form an accelerating potential within the spectrometer;

(c) striking the tip within the spectrometer with a series of laser pulses whose spot sizes on the tip are larger than 0.03 mm^2 in area in order to desorb ions of the molecules from the tip; and

(d) detecting the mass weights of the ions by their time of flight with a resolution of the molecular ion signal greater than 50 full width at half-maximum (FWHM) and displaying such detected mass weights.

11. A method in mass spectrometry to measure the mass of organic molecules with improved resolution, including the steps of:

(a) spraying a heat responsive matrix material through an electric field by electro-deposition on the tip of a probe to form a thin and even layer of the matrix material on the tip;

(b) applying the organic molecules to the matrix layer.

(c) placing the probe into one end of a time of flight mass spectrometer and applying a vacuum and an electric field to form an accelerating potential within the spectrometer;

(d) striking a spot of the probe tip within the spectrometer with a series of laser pulses to desorb ions of the molecules from the face of the tip; and

(e) detecting the mass weights of the ions by their time of flights to a resolution of the molecular ion signal of greater than 50 full width at half-maximum definition (FWHM) and displaying such detected mass weights.

12. A method as in claims 10 or 11 wherein said spot size is in the range of 0.03 to 3.0 mm^2 in area.

13. A method as in claims 10 or 11 wherein the area of said spot is in the range of 0.1–1 mm^2.

14. A method as in claims 10 or 11 wherein the molar ratio of organic molecules to matrix material is in the range of 1:100 to 1:10,000.

15. A method as in claims 10 or 11 wherein the accelerating electrical potential produces negative ions of the molecules.

16. A method as in claims 10 or 11 wherein the laser has an output pulse width in the 1–10 ns range.

17. A method as in claims 10 or 11 wherein the laser has a wavelength in the range of 200–600 nanometers.

18. A method as in claims 10 or 11 wherein the laser has a wavelength in the range of 330–550 nanometers.

19. A method in mass spectrometry to measure the mass of organic molecules with improved resolution, comprising:

a) forming a layer of organic molecules on a probe tip;

b) placing the probe tip into a time of flight mass spectrometer;

c) applying a vacuum and an electric field to form an accelerating potential within the mass spectrometer;

d) striking the probe tip within the mass spectrometer with a series of laser pulses providing a laser spot having an area in the range of from 0.1 to 1.0 mm^2;

e) activating a deflecting field in response to each of the laser pulses to deflect low weight ions passing through the deflecting field away from a detector;

f) deactivating the deflecting field in response to each of the laser pulses to pass high mass weight ions passing through the deflecting field to a detector; and

g) detecting the mass weight of the ions reaching the detector.

20. A method as in claim 19, further comprising:

providing a pair of plates to form the deflecting field; and

the steps of activating and deactivating the deflecting field comprise applying square wave pulses to at least one of the plates.

21. The method as in claim 20, further comprising:

grounding one of the pair of plates; and

applying the square wave pulses to the other of the pair of plates.

22. The method as defined in claim 19, further comprising:

displaying the detected mass weights of the detected ions.

23. The method as in claim 19, further comprising:

spraying a heat responsive matrix material through an electric field by electro-deposition on the probe tip to form a thin layer of matrix material on the probe tip; and

the step of forming a layer of organic molecules includes applying the organic molecules to the matrix layer.

24. A method as in claim 23, wherein the molar weight organic molecules to matrix material is in the range of from 1:100 to 1:10.000.

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